CAPROLACTAM

Data were last reviewed in IARC (1986) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

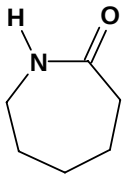
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 105-60-2
Chem. Abstr. Name: Hexahydro-2*H*-azepin-2-one
IUPAC Systematic Name: Hexahydro-2*H*-azepin-2-one
Synonyms: 2-Ketohexamethylenimine; 2-oxohexamethylenimine

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_6H_{11}NO$ Relative molecular mass: 113.16

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: White crystalline solid (American Conference of Governmental Industrial Hygienists, 1991)
(*b*) *Boiling-point*: 270°C (Lide, 1997)
(*c*) *Melting-point*: 69.3°C (Lide, 1997)
(*d*) *Solubility*: Very soluble in water, benzene, diethyl ether, and ethanol; soluble in methanol, tetrahydrofurfuryl alcohol, dimethylformamide, chlorinated hydrocarbons, and petroleum fractions (Budavari, 1996; Lide, 1997)
(*e*) *Vapour pressure*: 800 Pa at 120°C (American Conference of Governmental Industrial Hygienists, 1991)
(*f*) *Flash-point*: 125°C, open cup (Budavari, 1996)
(*g*) *Conversion factor*: $mg/m^3 = 4.6 \times ppm$

1.2 Production and use

Production in the United States in 1993 was reported to be 649 825 tonnes (United States International Trade Commission, 1994). Estimated production capacities of caprolactam in 1990 were reported as (thousand tonnes): United States, 640; western Europe, 860; eastern Europe, 895; Japan, 500; Latin America, 150; Asia, 290 (Fisher & Crescentini, 1992).

Caprolactam is used primarily in the manufacture of synthetic fibres and resins (especially nylon 6), bristles, film, coatings; synthetic leather, plasticizers and paint vehicles; as a cross-linking agent for polyurethanes; and in the synthesis of the amino acid lysine (Lewis, 1993).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES, 1997), approximately 25 000 workers in the United States were potentially exposed to caprolactam (see General Remarks). Occupational exposures to caprolactam may occur in the manufacture of the chemical and of polycaprolactam (nylon 6) fibres and resins.

1.3.2 *Environmental occurrence*

Caprolactam may be released to the environment during its manufacture and use in the preparation of resins and plastics (United States National Library of Medicine, 1997). It has been detected in surface water, groundwater and drinking-water (IARC, 1986).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 1 mg/m^3 as the 8-h time-weighted average threshold limit value for occupational exposures to caprolactam dust in workplace air and 23 mg/m^3 for the vapour. Similar values have been used as standards or guidelines in many countries (International Labour Office, 1991).

No international guideline for caprolactam in drinking-water has been established (WHO, 1993).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Caprolactam was tested for carcinogenicity in mice and rats by oral administration in the diet. No carcinogenic effect was observed (IARC, 1986).

3.1 Multistage protocols and preneoplastic lesions

Rat: A group of 15 male F344/DuCrj rats, six weeks of age, was administered a single intraperitoneal injection of 100 mg/kg bw *N*-nitrosodiethylamine (NDEA), followed by four twice weekly intraperitoneal injections of 20 mg/kg bw *N*-methyl-*N*-nitrosourea (MNU) during weeks 1 and 2 and administration of 0.1% *N*-bis(2-hydroxypropyl)nitrosamine in the drinking-water during weeks 3 and 4. The rats were then given 10 000 mg caprolactam [purity unspecified]/kg diet (ppm) for 16 weeks. A group of 30 rats was given basal diet after the first-step procedure and served as controls. In addition, five rats received vehicles without carcinogens during the first-step treatment period and were then given 10 000 mg caprolactam/kg diet (ppm) for 16 weeks. Animals were killed at week 20 and histological examination of most organs and any gross lesions and quantitation of glutathione *S*-transferase (placental form) (GST-P)-positive foci of the liver were performed. Caprolactam showed no modifying effect in any organ (Fukushima *et al*., 1991).

Two groups of 14 and 15 male Fischer 344 rats, six weeks of age, were administered a single intraperitoneal injection of 200 mg/kg bw NDEA in 9% (w/v) saline. After a two-week recovery period, rats were given either 10 000 mg caprolactam [purity unspecified]/kg diet (ppm) or basal diet for six weeks. At week 3, all rats were subjected to a two-thirds partial hepatectomy and killed at week 8. Quantitative analysis of GST-P-positive foci of the liver was performed. There were no significant differences in either the numbers or areas of GST-P-positive foci between the caprolactam-treated group and the controls (Hasegawa & Ito, 1992).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

The major urinary metabolites of caprolactam were identified in male Sprague-Dawley rats given 3% caprolactam in the diet for two to three weeks. Twenty-four-hour urine samples were collected during the final week and metabolites isolated by ion-exchange chromatography and characterized by infrared and nuclear magnetic resonance spectroscopy. The major metabolite (16% of the dose) was 4-hydroxycaprolactam or the corresponding free acid: this rearranges in acid to an equilibrium mixture of 6-amino-α-caprolactone and 6-amino-4-hydroxyhexanoic acid. A small amount of 6-aminohexanoic acid was also excreted (Kirk *et al.*, 1987).

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

Oral treatment of adult female Sprague-Dawley rats with 425 mg/kg bw caprolactam 21 and 4 h before killing resulted in a significant increase in serum alanine aminotransferase activity (33%), while hepatic ornithine decarboxylase activity and cytochrome P450 content were not changed significantly (Kitchin & Brown, 1989).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Caprolactam was evaluated for developmental toxicity in both rats and rabbits (Gad *et al*., 1987). Rats were dosed by gavage on days 6–15 of gestation with 0, 100, 500 or 1000 mg/kg bw per day. No skeletal anomalies or major malformations were observed in the pups, while, in the high-dose group, maternal survival rate and fetal viability were decreased. Rabbits were dosed by gavage on days 6–28 of gestation with 0, 50, 150 or 250 mg/kg bw per day. No embryotoxicity or teratogenicity was observed. In the groups dosed with 150 and 250 mg/kg bw per day, fetal weights were decreased and in the groups given 250 mg/kg bw there was an increased incidence of thirteen ribs.

In a three-generation reproduction study, Fischer 344 rats were given 0, 1000, 5000 and 10 000 mg caprolactam/kg diet (ppm) (Serota *et al*., 1988). Each generation was treated over a 10-week period. In both the parental generations and the offspring, reduced body weights were found in the high-dose groups. Otherwise, no treatment-related effect on gross appearance, gross pathology, survival rate or number of pups was observed. In some instances, significantly reduced body weights were also observed in adult animals receiving 5000 mg caprolactam/kg diet.

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

The genetic and related effects of caprolactam have been reviewed (Ashby & Shelby, 1989; Brady *et al*., 1989)

Caprolactam gave negative results across a wide range of in-vitro and in-vivo short-term tests. It did not induce mutation in *Salmonella typhimurium* or gene mutation or aneuploidy in *Aspergillus nidulans* in the presence or absence of an exogenous metabolic activation system. In *Saccharomyces cerevisiae*, no gene conversion was induced and

Table 1. Genetic and related effects of caprolactam

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
SAF, *Salmonella typhimurium* TM677, forward mutation	–	–	500	Liber (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	25000	Greene *et al*. (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500	Baker & Bonin (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2500	Matsushima *et al*. (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2500	Rexroat & Probst (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000	Zeiger & Haworth (1985)
SA2, *Salmonella typhimurium* TA102, reverse mutation	–	–	500	Baker & Bonin (1985)
SA2, *Salmonella typhimurium* TA102, reverse mutation	–	–	2500	Matsushima *et al*. (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	25000	Greene *et al*. (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	2500	Rexroat & Probst (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5000	Zeiger & Haworth (1985)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	25000	Greene *et al*. (1979)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	2500	Rexroat & Probst (1985)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	25000	Greene *et al*. (1979)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	2500	Rexroat & Probst (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	25000	Greene *et al*. (1979)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	Baker & Bonin (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	2500	Matsushima *et al*. (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	2500	Rexroat & Probst (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000	Zeiger & Haworth (1985)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	500	Baker & Bonin (1985)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	2500	Matsushima *et al*. (1985)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	5000	Zeiger & Haworth (1985)
SCG, *Saccharomyces cerevisiae* D7, gene conversion	–	–	5000	Arni (1985)
SCG, *Saccharomyces cerevisiae* JD1, gene conversion	–	–	2000	Brooks *et al*. (1985)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
SCG, *Saccharomyces cerevisiae* PV-2 and PV-3, gene conversion	–	–	1000	Inge-Vechtomov *et al*. (1985)
SCG, *Saccharomyces cerevisiae* D7-144, gene conversion	+	(+)	400	Mehta & von Borstel (1985)
SCG, *Saccharomyces cerevisiae* D7, gene conversion	–	–	2000	Parry & Eckardt (1985a)
SCH, *Saccharomyces cerevisiae* D7, homozygosis	–	–	5000	Arni (1985)
SCH, *Saccharomyces cerevisiae* PV4a and PV4b, homozygosis	–	–	1000	Inge-Vechtomov *et al*. (1985)
SCH, *Saccharomyces cerevisiae* D6 and D61-M, homozygosis	–	–	5000	Parry & Eckardt (1985b)
SCH, *Saccharomyces cerevisiae* D61-M, homozygosis	–	NT	15000	Zimmermann *et al*. (1985)
SCF, *Saccharomyces cerevisiae* D5, forward mutation	–	NT	2000	Ferguson (1985)
SCF, *Saccharomyces cerevisiae* PV-1, forward mutation	–	–	1000	Inge-Vechtomov *et al*. (1985)
SCR, *Saccharomyces cerevisiae* D7, reverse mutation	–	–	5000	Arni (1985)
SCR, *Saccharomyces cerevisiae* PV2 and PV3, reverse mutation	–	–	1000	Inge-Vechtomov *et al*. (1985)
SCR, *Saccharomyces cerevisiae* XV185-14C, reverse mutation	+	+	100	Mehta & von Borstel (1985)
SCR, *Saccharomyces cerevisiae* RM52, reverse mutation	–	–	800	Mehta & von Borstel (1985)
SCR, *Saccharomyces cerevisiae* D7, D6 and D61-M, reverse mutation	–	–	2000	Parry & Eckardt (1985a,b)
SZF, *Schizosaccharomyces pombe*, forward mutation	–	–	1900	Loprieno *et al*. (1985)
ANF, *Aspergillus nidulans*, forward mutation	–	NT	1000	Carere *et al*. (1985)
SCN, *Saccharomyces cerevisiae* D6 and D61-M, aneuploidy	–	–	5000	Parry & Eckardt (1985b)
SCN, *Saccharomyces cerevisiae* D61-M, aneuploidy	(+)	NT	7500	Zimmermann *et al*. (1985)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
ANN, *Aspergillus nidulans*, aneuploidy	–	NT	500	Carere *et al*. (1985)
DMG, *Drosophila melanogaster*, genetic crossing over/recombination	–		565 feed	Vogel (1985)
DMG, *Drosophila melanogaster*, genetic crossing over/recombination	–		5000 feed	Wurgler *et al*. (1985)
DMM, *Drosophila melanogaster*, somatic mutation	+		45000 feed	Fujikawa *et al*. (1985)
DMM, *Drosophila melanogaster*, somatic mutation	(+)		565 feed	Vogel (1985)
DMM, *Drosophila melanogaster*, somatic mutation	+		1000 feed	Wurgler *et al*. (1985)
DMM, *Drosophila melanogaster*, somatic mutation (mitotic recombination (SMART) test)	(+)		425 feed	Vogel (1989)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	(+)		1700 feed	Vogel (1989)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		15000 ppm inj	Foureman *et al*. (1994)
DIA, DNA single-strand breaks, Fischer 344 rat hepatocytes *in vitro*	–	NT	3390	Bradley (1985)
DIA, DNA single-strand breaks, Chinese hamster ovary CHO cells *in vitro*	–	–	11300	Douglas *et al*. (1985)
DIA, DNA single-strand breaks, Chinese hamster ovary CHO cells *in vitro*	–	–	NG	Lakhanisky & Hendrickx (1985)
URP, Unscheduled DNA synthesis, male Fischer 344 rat primary hepatocytes *in vitro*	–	NT	113	Probst & Hill (1985)
URP, Unscheduled DNA synthesis, male Fischer 344 rat primary hepatocytes *in vitro*	–	NT	1000	Williams *et al*. (1985)
GCO, Gene mutation, Chinese hamster ovary CHO cells *in vitro*	–	–	5000	Greene *et al*. (1979)
GCO, Gene mutation, Chinese hamster ovary CHO cells *in vitro*	–	–	2000	Zdzienicka & Simons (1985)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	–	–	3000	Fox & Delow (1985)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	–	–	1000	Kuroda *et al*. (1985)
G9O, Gene mutation, Chinese hamster lung V79 cells, ouabain resistance *in vitro*	NT	–	113	Kuroki & Munakata (1985)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	–	11000	Amacher & Turner (1985)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	–	15000	Knaap & Langebroek (1985)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	–	5000	Myhr *et al*. (1985)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	–	10000	Oberly *et al*. (1985)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	NT	1000	Styles *et al*. (1985)
G51, Gene mutation, mouse lymphoma L5178Y cells, ouabain resistance *in vitro*	–	–	200	Garner & Campbell (1985)
G51, Gene mutation, mouse lymphoma L5178Y cells, *hprt* locus *in vitro*	–	–	200	Garner & Campbell (1985)
G51, Gene mutation, mouse lymphoma L5178Y cells, *hprt* locus *in vitro*	–	–	15000	Knaap & Langebroek (1985)
GIA, Gene mutation, mouse BALB/c–3T3 cells, ouabain resistance *in vitro*	NT	?	15000	Matthews *et al*. (1985)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	1130	Douglas *et al*. (1985)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	5000	Gulati *et al*. (1985)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	5000	Lane *et al*. (1985)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	17000	Natarajan *et al*. (1985)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	10600	Norppa & Järventaus (1989)
SIC, Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	–	–	5650	van Went (1985)
SIR, Sister chromatid exchange, Wistar rat liver cell line (RL_4) *in vitro*	–	NT	1000	Priston & Dean (1985)
MIA, Micronucleus test, Chinese hamster ovary CHO cells *in vitro*	–	–	113	Douglas *et al*. (1985)
CIC, Chromosomal aberrations, Chinese hamster lung CH1-L cells *in vitro*	–	NT	2000	Danford (1985)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	–	5000	Gulati *et al*. (1985)
CIC, Chromosomal aberrations, Chinese hamster lung CHL cells *in vitro*	–	?	10000	Ishidate & Sofuni (1985)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	–	17000	Natarajan *et al*. (1985)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	–	2500	Palitti *et al*. (1985)
CIR, Chromosomal aberrations, Wistar rat liver RL_4 cells *in vitro*	–	NT	1000	Priston & Dean (1985)
AIA, Aneuploidy, Chinese hamster lung CH1-L cells *in vitro*	–	NT	2000	Danford (1985)
TBM, Cell transformation, mouse BALB/c–3T3 cells	–	+	2500	Matthews *et al*. (1985)
TCM, Cell transformation, mouse C3H 10T½ cells	(+)	–	4570	Lawrence & McGregor (1985)
TCM, Cell transformation, mouse C3H 10T½ cells	–	NT	1000	Nesnow *et al*. (1985)
TCS, Cell transformation, Syrian hamster embryo, clonal assay	+	NT	10	Barrett & Lamb (1985)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
TCS, Cell transformation, Syrian hamster embryo, clonal assay	–	NT	1000	LeBoeuf *et al*. (1989)
TCS, Cell transformation, Syrian hamster embryo, clonal assay	?	NT	300	Sanner & Rivedal (1985)
TFS, Cell transformation, Syrian hamster embryo, focus assay	–	NT	6000	Greene *et al*. (1979)
TRR, Cell transformation, RLV/Fischer rat cells	–	NT	50	Suk & Humphreys (1985)
T7S, Cell transformation, SA7/Syrian hamster embryo cells	–	NT	7000	Greene *et al*. (1979)
T7S, Cell transformation, SA7/Syrian hamster embryo cells	–	NT	5000	Hatch & Anderson (1985)
GIH, Gene mutation, human lymphocytes *in vitro*	–	–	8000	Crespi *et al*. (1985)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	–	–	1000	Obe *et al*. (1985)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	+	270	Howard *et al*. (1985)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	?	NT	7500	Kristiansen & Scott (1989)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	+	4250	Norppa & Jarventaus (1989)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	(+)	(+)	5500	Sheldon (1989a)
AIH, Aneuploidy, human lymphocytes *in vitro*	+	+	2125	Norppa & Jarventaus (1989)
DVA, DNA single-strand breaks, male Fischer 344 rat hepatocytes *in vivo*	–		750 po × 1	Bermudez *et al*. (1989)
DVA, DNA single-strand breaks/alkaline-labile sites, Sprague-Dawley rat hepatocytes *in vivo*	–		425 po × 2	Kitchin & Brown (1989)
UPR, Unscheduled DNA synthesis, male Fischer 344 rat hepatocytes *in vivo*	–		750 po × 1	Bermudez *et al*. (1989)
UVR, Unscheduled DNA synthesis, Fischer 344 rat spermatocytes *in vivo*	–		750 po × 1	Working (1989)
MST, Mouse spot test, (C57BL × T)F_1 mice	?		500 ip × 1	Fahrig (1989)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
MST, Mouse spot test $(T \times HT)F_1$ mice	?		500 ip × 1	Neuhauser-Klaus & Lehmacher (1989)
SVA, Sister chromatid exchange, $B6C3F_1$ mouse bone marrow *in vivo*	–		700 ip × 1	McFee & Lowe (1989)
MVM, Micronucleus test, ICR/JCL mouse bone marrow *in vivo*	–		500 ip × 1	Ishidate & Odagiri (1989)
MVM, Micronucleus test, C57BL/6J mouse bone marrow *in vivo*	–		700 po × 1	Sheldon (1989b)
CBA, Chromosomal aberrations, $B6C3F_1$ mouse bone marrow *in vivo*	–		1000 po × 1	Adler & Ingwersen (1989)
CBA, Chromosomal aberrations, $B6C3F_1$ mouse bone marrow *in vivo*	–		700 ip × 1	McFee & Lowe (1989)
SPM, Sperm morphology, $B6C3F_1$ mice *in vivo*	–		1125 po × 5	Salamone (1989)
ICR, Inhibition of cell communication, Chinese hamster lung V79/4K-1 and V79-M13 cells *in vitro*	–	NT	400	Scott *et al*. (1985)
ICR, Inhibition of cell communication, Chinese hamster lung V79 cells *in vitro*	–	NT	2250	Umeda *et al*. (1985)

[a] +, positive; (+), weakly positive; –, negative; NT, not tested; ?, inconclusive

[b] HID, highest ineffective dose; LED, lowest effective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; NG, not given; inj, injection; po, oral; ip, intraperitoneal

there was no induction of point mutations in three of four studies or aneuploidy in one of two studies. In *Drosophila melanogaster*, it induced somatic cell mutations in four studies and a marginal increase in sex-linked recessive lethal mutations in one of two studies.

Neither DNA single-strand breaks nor unscheduled DNA synthesis were induced in cultures of rat primary hepatocytes and DNA strand breaks were not induced in Chinese hamster ovary cells treated with caprolactam. Gene mutations were not induced in Chinese hamster ovary, lung V79 or mouse lymphoma L5178Y cells *in vitro*. Caprolactam did not increase the frequency of sister chromatid exchanges, micronuclei, chromosomal aberrations or aneuploidy in Chinese hamster cell cultures nor did it inhibit intercellular communication. Marginally positive results were reported in tests for morphological transformation using mouse BALB/c-3T3, C3H 10T½, and Syrian hamster embryo cells, while results from virally enhanced cell transformation tests were negative.

Caprolactam did not induce gene mutations in human lymphoblastoid AHH-1 cells or sister chromatid exchanges in human lymphocyte cultures, but it did increase the frequency of chromosomal aberrations in four studies and, in a single study, aneuploidy in human lymphocytes *in vitro*.

Caprolactam treatment *in vivo* did not increase DNA single-strand breaks in hepatocytes or unscheduled DNA synthesis in spermatocytes of rats, did not induce sister chromatid exchanges, micronuclei or chromosomal aberrations in mouse bone marrow and did not induce morphological abnormalities in mouse sperm. Inconclusive results were reported in two mouse spot test studies for gene mutations.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to caprolactam, a monomer used in high volume, can occur in its manufacture and the manufacture of nylon 6. It has been detected in surface water, groundwater and drinking-water.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Caprolactam was tested for carcinogenicity by oral administration in the diet of mice and rats. No increase in the incidence of tumours was observed. Caprolactam was also tested for promoting effects in two multistage studies in male rats. In one, oral administration of caprolactam in the diet after treatment with several carcinogens showed no modifying effect on carcinogenicity in any organ or on glutathione *S*-transferase (placental form) (GST-P)-positive foci of the liver. In the other study, oral administration of caprolactam in the diet with a two-thirds partial hepatectomy after treatment with *N*-nitrosodiethylamine did not increase the numbers or areas of GST-P-positive foci in the liver.

5.4 Other relevant data

Caprolactam is metabolized in rats to a number of metabolites including 4-hydroxycaprolactam. In rats, it exhibits some hepatotoxicity at high doses.

Caprolactam was not mutagenic to rodents *in vivo.* It induced chromosomal aberrations and aneuploidy in human lymphocytes *in vitro*, but no other evidence of mutagenicity has been found in a variety of tests with rodent cell cultures. Results for morphological transformation in mammalian cells were inconclusive. Caprolactam was mutagenic in somatic and to a lesser degree to germ cells in *Drosophila melanogaster*. Caprolactam was not genotoxic in bacteria.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of caprolactam were available.

There is *evidence suggesting a lack of carcinogenicity* of caprolactam in experimental animals.

Overall evaluation

Caprolactam is *probably not carcinogenic to humans (Group 4).*

6. References

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