FOREWORD INTRODUCITON

3-Pyridinecarboxamide (nicotinamide)

CAS N°: 98-92-0

SIDS Initial Assessment Report

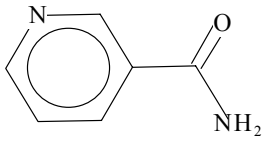
For

SIAM 15

Boston, Massachusetts, 22-25 October 2002

1.	**Chemical Name:**	3-Pyridinecarboxamide (nicotinamide)
2.	**CAS Number:**	98-92-0
3.	**Sponsor Country:**	Switzerland
		National SIDS Contact Point in Sponsor Country: Dr. Georg Karlaganis Swiss Agency for the Environment, Forests and Landscape CH-3003 Berne, Switzerland e-mail: georg.karlaganis@buwal.admin.ch
4.	**Shared Partnership with:**	
5.	**Roles/Responsibilities of the Partners:**	
•	Name of industry sponsor /consortium	
•	Process used	
6.	**Sponsorship History**	
•	How was the chemical or category brought into the OECD HPV Chemicals Programme ?	This substance is evaluated under the OECD HPV Chemicals Programme and is submitted for first discussion at SIAM 15. No testing (X) Testing ( )
7.	**Review Process Prior to the SIAM:**	
8.	**Quality check process:**	
9.	**Date of Submission:**	13 August 2002
10.	**Date of last Update:**	
11.	**Comments:**	

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	98-92-0
Chemical Name	3-Pyridinecarboxamide (nicotinamide)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Nicotinamide is a vitamin, an essential constituent for the synthesis of pyridine coenzymes in mammalian systems. The substance can be synthetised directly in the body from the aminoacid tryptophan. In humans exogeneous nicotinamide is easily absorbed from the gastro-intestinal tract. In other species it may be deamidated to nicotinic acid by intestinal micro-organisms before entering the systemic circulation. The substance can be incorporated into NAD(P) either directly or after deamidation or metabolised and excreted in urine. The primary metabolite in both humans and rats is N-methylnicotinamide.

The acute toxicity of nicotinamide after oral administration or dermal application is very low: oral LD_{50} 3-7 g/kg bw in rodents and dermal LD_{50} >2000 mg/kg bw in rabbits. Skin irritation studies indicate that nicotinamide has no potential to irritate the skin. Nicotinamide is an eye irritant. Evidence from human exposure indicates that nicotinamide is not a skin sensitiser.

In a 4-week oral toxicity study male rats dosed with 215 and 1000 mg/kg bw showed a significant decrease in body weight gain and food consumption during part of the treatment period. Liver weight was increased accompanied histopathologically by mild liver centrilobular hypertrophy in all treated animals. These effects were considered to be an adaptive response to nicotinamide treatment. In females at the high dose group extramedullary haematopoiesis was reported. The NOAEL derived from this study is 215 mg/kg bw. In this study no effects on male and female gonads were found.

A developmental toxicity test was performed in rats with nicotinic acid, which has a similar physiological function as nicotinamide and comparable kinetics as nicotinamide in rats. The NOAEL for maternal toxicity derived from this study was 200 mg/kg bw/d based on effects on body weight (equivalent to 198 mg/kg bw/d for nicotinamide). The NOAEL on reproduction toxicity and developmental toxicity is 200 mg/kg bw/d (equivalent to 198 mg/kg bw/d nicotinamide) based on the significantly decreased placental and pup body weight (males only). No teratogenic effects were observed.

Nicotinamide is considered not mutagenic in bacterial strains. No chromosomal effects in mammalian cells were reported. In an *in vivo* micronucleus test no clastogenic effects were seen. Thus nicotinamide is not mutagenic.

In humans nausea with or without vomiting was the main effect after acute exposure and generally seen after doses in excess of 5 g/day. No persisting effects were reported.

Environment

Nicotinamide is a solid with a vapour pressure of 31.4 hPa (at 25ºC), a water solubility of 691-1000 g/L and a Log K_{ow} of -0.38 (at 22°C). It has a calculated half-life for photo-oxidation of 2.23 days in the atmosphere. Nicotinamide will partition primarily to water (Mackay level III modelling). No hydrolysis is expected based on the stability of the amide bond. Nicotinamide is readily biodegradable (100% within one week). Based on the log K_{ow} nicotinamide is not expected to bioaccumulate (calculated BCF 3.162). It has a low potential for sorption to soil (predicted log Koc 0.97).

The 96-hour LC_{50} in fish for nicotinamide is >1000 mg/L The 24-hour EC_{50} for daphnia is >1000 mg/L. In a test

with algae (*Scenedesmus subspicatus*, 72-hours exposure) virtually no growth was seen during the first 24 hours. The 72-hour E_bC_{50} and E_rC_{50} were >1000 mg/L. The EC_{10} for the inhibition of micro-organisms is 4235 mg/L.

Exposure

Nicotinamide can be found as a dietary supplement in food and feed and in cosmetics. Consumers may be exposed to nicotinamide by the oral and dermal routes of exposure. There is a potential for occupational exposure through inhalation and skin contact.

There is potential exposure for the aquatic compartment arising from the production and processing of nicotinamide.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

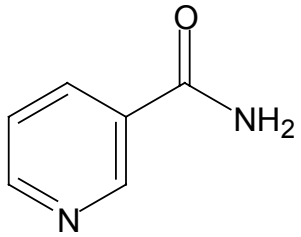
The chemical is currently of low priority for further work based on a low hazard potential. However it is noted that the substance is an eye irritant.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 98-92-0
Chemical Name: 3-Pyridinecarboxamide
Nicotinamide
Molecular Formula: $C_6H_6N_2O$



Structural Formula:
Molecular Weight: 122.13
Synonyms: Niacinamide, pyridine-3-carboxamide

1.2 Purity/Impurities/Additives

Purity: ≥ 99.00% (ref. 117)

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value
Physical state	Solid
Form	Crystalline powder (ref. 117)
Colour	White (ref. 117)
Odour	Odourless (ref. 117)
Melting point	127-131°C (ref. 1, 2, 117, 118)
Boiling point	224°C (2000 Pa) (ref. 117) or 157°C (0.066 Pa) (ref. 1)
Density	1.4 g/cm^3 (ref. 1) (Bulk density 500-700 kg m^3, ref. 117)
Vapour pressure	31.4 hPa (25°C) (ref. 2)
Water solubility	691-1000 g/L (ref.117, 118)
Partition coefficient n-octanol/water (log value)	-0.38 (22°C) (ref. 3)

The values above are mainly from handbooks. Solubility in water is high. The Log Pow was determined according to OECD 107.

General Information

Nicotinamide is a water-soluble vitamin of the B complex, which together with nicotinic acid belongs to vitamin B3 or vitamin PP. Nicotinamide and nicotinic acid are also called niacinamide and niacin, respectively. However, the term of niacin in the open literature often refers to both substances. Sources of niacin are among others grains, meat and milk. Deficiency of this vitamin leads initially to non-specific symptoms like lassitude, anorexia, weakness, indigestion and irritability, progressing eventually to pellagra, which is characterised by dermatitis, diarrhoea and dementia (ref. 49). In industrialised countries, pellagra is rarely seen. It is often the result of the vitamin- and protein-deficient diets of alcoholics or seen in patients with liver cirrhosis, chronic diarrhoea, diabetes mellitus, neoplasias and prolonged infectious diseases (ref. 110). Deficiency can be corrected by intake of so called niacin equivalents (nicotinic acid, nicotinamide or their precursor tryptophan).

Nicotinamide is the active form that acts as constituent of the enzyme cofactors NAD (nicotinamide adenine dinucleotide) and NADP (nicotinamide adenine dinucleotide phosphate) (pyridine nucleotides). These function as electron carriers in cell metabolism of carbohydrates, fatty acids and amino acids.

2 GENERAL INFORMATION ON EXPOSURE

Estimated Production or Import Volume

The worldwide production is estimated to amount to about 15’000 tonnes per year (data Lonza 2001). The total quantity annually produced or imported into Europe elevates to about 5’000 tonnes.

Uses

Nicotinamide is used in human and animal nutrition to enrich various foods (e.g. bakery and cereals), drinks or feed. As a dietary supplement it is also incorporated in tablets and capsules.

Nicotinamide is also used in cosmetics as hair and skin conditioning agent (ref. 78).

In the USA nicotinamide is a constituent of household solvent and cleaning products and paints that may be used by consumers (WESTAT Inc., 1987)

Experimental therapeutical applications are reported for the treatment of chronic alcoholism and schizophrenia (ref. 49). Nicotinamide has also been tested as radio-sensitiser in the radio therapeutic treatment of cancer to enhance radiation damage (ref. 64, 69). The most promising use seems however to be in the prevention and control of diabetes type I (ref. 36, 119).

Table 2 Overview of Uses (estimations)

TYPE OF END USE	% OF PRODUCTION VOLUME (approx.)	SPECIFIC APPLICATIONS
Dietary supplement, food	30%	Enrichment of various foods and drinks
	10%	In tablets and capsules
Dietary supplement, feed	50%	In poultry, swine, fish, dairy nutrition etc
Cosmetics	10%	Hair and skin conditioning agent (Weight fraction in products 0.002).
Therapeutics	negligible	Treatment of chronic alcoholism
		Animal pharmaceuticals (Weight fraction in products 0.001)
		Other, for research only

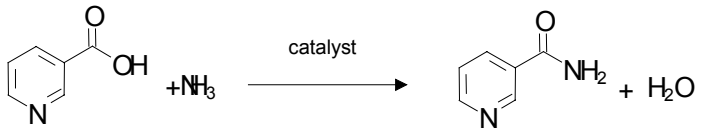
Manufacturing process

Nicotinamide can be synthesized industrially by two ways, either starting from nicotinic acid or starting from 3-cyanopyridine.

A. Description of the process starting from nicotinic acid

Nicotinic acid is melted and reacted with ammonia gas to yield nicotinamide. The reaction is catalysed by the presence of ammonium salts. After distillation, nicotinamide is dissolved in water, purified by the addition of activated carbon, filtered, recrystallized and centrifuged. The nicotinamide contained in the mother liquor is reclaimed by a special recovery operation. The wet pure nicotinamide filter cake is dried under vacuum in a rotary vacuum drier.

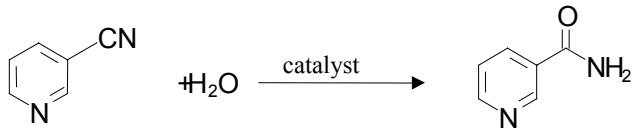
Chemical reaction:



B. Description of the process starting from 3-cyanopyridine

A buffered solution of 3-cyanopyridine in water is hydrolysed to nicotinamide in the presence of a catalyst. The resulting solution is purified over activated carbon, filtered and then concentrated in a evaporator. The concentrated nicotinamide solution is dried under vacuum.

Chemical reaction:



3-cyanopyridinene water nicotinamide

Table 3 Possible Routes of Exposure

Environmental exposure	**Aquatic**	**Production**
	Aquatic	Processing/ Industrial use
	Aquatic	Consumer use
Consumer exposure	Dermal	Cosmetics
	Oral	Pharmaceuticals
	Oral	Food (supplement)
Worker exposure	Dermal/inhalation	Production
	Dermal/inhalation	Formulation/Processing

2.1 Environmental Exposure and Fate

Nicotinamide is very soluble in water, has a vapour pressure of 31.4 hPa at 25°C and a calculated Henry's Law constant of 0.555. The Henry's Law constant was calculated using the EUSES model. The following values were used in environmental fate and distribution modelling:

Parameter	**Nicotinamide**	**Discussion**
Vapour pressure	31.4 hPa	Measured value from literature
Solubility	691000 mg/L	Measured value from literature
Log K_{ow}	-0.38	Based on a test according to OECD 107
Log Koc	0.97	See section 2.1.4
Biodegradability	Ready biodegradable	Based on a test according to OECD 301E

2.1.1 Sources of Environmental Exposure

Production of nicotinamide takes place mainly in a closed process. During production and processing (industrial use) very small amounts of nicotinamide may be released to the aquatic compartment.

2.1.2 Photodegradation

The calculated half-life for the photo-oxidation (reaction with hydroxyl radicals) of nicotinamide in air is 2.23 days (Epiwin vs 3.10).

2.1.3 Stability in Water

The stability of nicotinamide in water was not assessed in a test. This is considered acceptable, since the only bond in the molecule that would be hydrolysable, the amide bond, is not likely to hydrolyse under environmental conditions.

The stability of the amide group is confirmed by modelling (HYDROWIN, Epiwin 3.10). The hydrolysis rate was stated to be extremely slow (t1/2> 1 year).

2.1.4 Transport between Environmental Compartments

Level III fugacity modelling shows about 99.8 % of nicotinamide ends up in the water phase. Negligible amounts will be distributed towards soil, sediment and air.

From the log K_{ow} value the log K_{oc} was determined to be 0.97 (EU Technical Guidance Document QSAR for non-hydrophobes and amides, chapter 4 section 4.3 [1]) indicating a low potential for sorption to soil. Other QSAR programs may give a different outcome, due to another calculation method.

The distribution in a sewage treatment plant has been estimated using the SimpleTreat model based on the values mentioned in section 2.1.

Fraction degraded [%}	87.2
Fraction to air [%]	0.24
Fraction to water [%]	12.6
Fraction to sludge [%]	0.009

Conclusion: Based on the relevant physical-chemical properties, the substance is expected to partition primarily to water. Nicotinamide is readily biodegradable. Mackay level III modelling shows 99.8% in water. The Simple Treat model predicts that nicotinamide will undergo a substantial degree of degradation in the sewage treatment plant.

2.1.5 Biodegradation

Nicotinamide was found to be readily biodegradable in a modified OECD screening test (ref. 4). In this test performed essentially in accordance with OECD 301E the substance degraded for 100% within one week (DOC removal).

Conclusion: The compound is readily biodegradable.

2.1.6 Bioaccumulation

The calculated bioconcentration factor is 3.162 (EPIWIN vs 3.10).

Conclusion: Based on Log K_{ow} of –0.38 from which the BCF of 3.162 is calculated, nicotinamide is not expected to bioaccumulate.

[1] LogKoc = 0.52 logKow + 1.02 (non-hydrophobes)

Log Koc = 0.33 logKow + 1.25 (amides)

2.2 Human Exposure

Nicotinamide is naturally present in animal products, whole cereals, nuts and legumes (ref. 33).

Studies demonstrate that minimum requirement for niacin equivalents (from all sources) to prevent pellagra ranges from 4.4 to 5.5 mg/1000 kcal (ref. 33), which corresponds to approximately 8-13 mg daily. The Recommended Dietary Allowance for adults is 6.6 mg niacin per 1000 kcal, with not less than 13 mg daily (ref. 110)

Since nicotinamide is present in foodstuffs and is used as a dietary supplement, direct consumer exposure is anticipated

Deficiencies due to unbalanced diet, excessive athletic training or malabsorption can be treated with nicotinamide at dosages up to 250 mg/day . No side effects are described in the literature up to this dose (ref. 49).

Experimental applications at therapeutical doses are reported in section 3.1.3.2.

As nicotinamide is also used in cosmetics, dermal exposure of consumers needs to be considered.

Potential occupational exposure during production and formulation is anticipated via the dermal and inhalatory route)

For occupational exposure to the nicotinamide, no specific exposure limit was derived.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

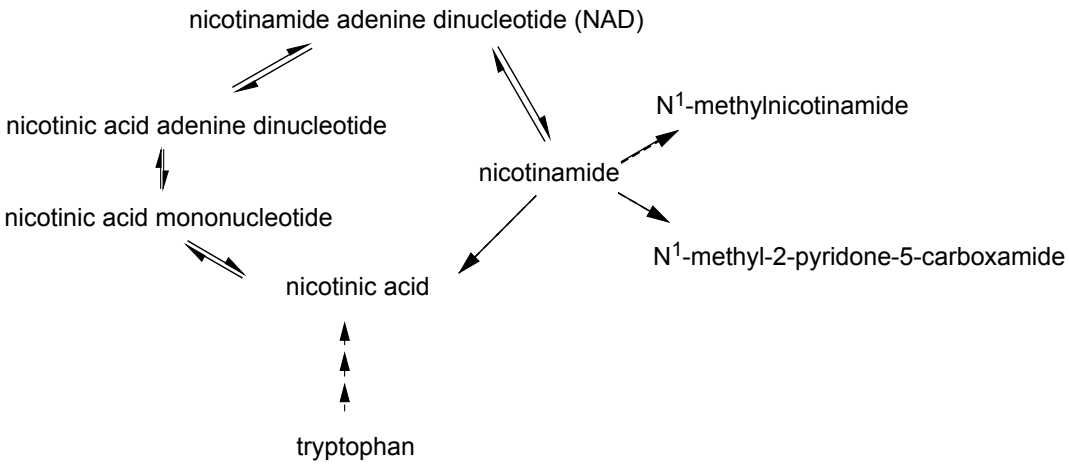
3.1.1 Toxicokinetics, Metabolism and Distribution

Studies in Animals

There is a large body of literature on metabolism of nicotinamide, nicotinic acid and tryptophan. Valuable reviews are given in references 33, 67,103, 112 and 113.

The two vitamers nicotinic acid and nicotinamide may be incorporated into the pyridine nucleotides coenzymes NAD(P) by different pathways (ref. 103). The use of exogeneous nicotinamide and nicotinic acid is limited and the main NAD(P) precursor is the amino acid tryptophan.

Nicotinamide is found in food either as constituent of the coenzyme NAD or in its free form. It is released from NAD in the intestinal mucosa by enzymatic hydrolysis.



Uptake

Nicotinic acid is absorbed by a combination of a sodium-independent carrier (at low concentrations) and diffusion (at high concentrations) (ref. 33, 103). In several species nicotinamide may be deamidated by the intestinal micro flora and the formed nicotinic acid is absorbed (ref. 67, 103, 108, 109). This is the case for rat, rabbit, guinea-pig, pig and horse. In man, dog and cat no deamidase activity by intestinal micro-organisms has been reported (ref. 103). Absorption of the amide is more rapid compared to the acid (ref. 49).

No data on uptake via the dermal and inhalation route are available.

Distribution

Nicotinamide is the primary circulating form of the vitamin (ref. 33). It is transported to tissues where NAD is locally synthesised and used (ref. 67). Nicotinamide readily passes the blood-brain barrier and is taken up by the brain cells by a high-affinity transport system (ref. 49). In the rat, the liver mitochondrial fraction, pancreatic β-cells, erythrocytes and cells of the testis prefer nicotinamide as substrate for the synthesis of NAD(P). Liver and kidney cells prefer nicotinic acid as substrate (ref. 103). In pregnant mice nicotinamide was detected in foetus at concentration about 5 times higher than in the maternal blood, whereas the metabolite nicotinic acid was not detected (ref. 55).

In rats intraperitoneal administration (2-3 times with intervals of 7-10 hours) of 500 mg nicotinamide/kg bw leads to increased amounts of nicotinic acid in the liver (up to 85% increase) (ref. 80). In another study the NAD-concentration in livers of rats dosed orally for 3 weeks (1, 10 and 100 mg/kg bw) was increased up to 50-fold in the highest dose group (compared to control values) (ref. 74). A similar increase was seen for the main metabolites N^1-methyl nicotinamide (NMN) and methyl-2-pyridione-5-carboxamide (2-PYR) in urine, but not for nicotinic acid (ref. 74). In mice receiving nicotinamide (100-1000 mg/kg i.p. as a single dose) peak plasma levels were reached quickly and half-life was about 2 hours (ref. 63).

Metabolism

When entering the systemic circulation the substance can be methylated and excreted via urine or deamidated (mostly in the liver) to form nicotinic acid and recycled to coenzyme synthesis (ref. 91). 60% of the deamidase activity is located in the microsomal fraction of the cells (ref. 104, 105).

In rat liver increased amounts of the methyl metabolite were found after repeated administration of nicotinamide. Methylation may lead to methyl deficiency as is reflected in low levels of choline as

methyl source found in the liver (ref. 71). In mice nicotinamide-N-oxide was found to be the main metabolite in plasma (ref. 91).

A single injection or 3 successive injections of nicotinamide (500 mg/kg bw) increased NADPH-cytochrome *c* reductase and aniline hydroxylase activities of rat liver microsomes without changing cytochrome P-450 content (ref. 80). Oral administration of nicotinamide for 2 weeks resulted in significant increase in cytochrome P-450, indicating nicotinamide as an inducer of cytochrome P-450 although its potency was weak (ref. 80, 103). A clear influence of sex on the alteration of the amount of microsomal mixed function oxidase in rat liver by nicotinamide was found (ref. 34). Several other publications show an influence of nicotinamide on mixed function oxidases in the liver of rodents (ref. 26, 70)

Excretion

Major urinary metabolites are N^1-methyl-nicotinamide and its oxidation product N^1-methyl-2-pyridone-5-carboxyamide. N^1-methyl-4-pyridone-3-carboxyamide and nicotinamide-N-oxide are also found in smaller quantities (ref. 49, 71, 110).

After oral administration the amount of N^1-methylnicotinamide excreted in the urine reached 100% in dog and, 30-50% in rats and humans. In man another 35-45% was found as 2-pyridone (N^1-methyl-2-pyridone-5-carboxyamide), in pig 10% and in rat 3-5% (ref. 103). The urinary excretion of unaltered nicotinamide increased sharply when single high doses were given (ref. 49, 74). The metabolites identified in urine were the same for both the acid and the amide, but differed quantitatively after single and repeated administration. An increase was seen for the main metabolites N^1-methyl nicotinamide (NMN) and methyl-2-pyridione-5-carboxamide (2-PYR) in urine after oral dosing for 3 weeks (1, 10 and 100 mg/kg bw), but not for nicotinic acid (ref. 74). Nicotinuric acid was found in urine after nicotinic acid administration, but also after large doses of nicotinamide (route probably via nicotinic acid) (ref. 49). In general, excretion of the amide (and its metabolites) tends to be more extensively compared to the acid (ref. 33).

Urinary N^1-methylnicotinamide excretion in rats treated daily with 0, 60, 200 or 600 mg/kg bw/d i.p. for 5 weeks increased in a time and dose dependent way (ref. 71).

Conclusion: Nicotinamide may deamidated to nicotinic acid by intestinal micro-organisms before entering the systemic circulation. This process appears to be species dependent. Nicotinamide is easily taken up from the gastro-intestinal tract. The substance can be incorporated into NAD(P) either directly or after deamidation or metabolised and excreted in urine.

Studies in Humans

In human volunteers (n=6) given a single dose of nicotinamide (3-9 g) as a tablet or in a liquid form plasma peak concentration (C_{max}) was between 0.3 and 1.7 µmol/ml and was reached after 0.5-3.0 hours (T_{max}) (ref. 92). Similar values were found in patients who received 80mg/kg bw nicotinamide during radiotherapy for 12 consecutive days (T_{max} = 0.8-4 h; C_{max} = 0.5-1.4 µmol/ml; $T_{1/2}$ = 7.1 h, ref. 64). In patients, that received nicotinamide daily (oral administration of 80 mg/kg bw/d during 5-7 weeks) a C_{max} of > 0.7 µmol/ml was found. Maximum plasma concentrations were reached within 0.25-3 hours after administration (ref. 69).

In a group of patients with superficial recurrent or metastatic cancer, plasma nicotinamide levels were dose dependent, showing a maximum 30 minutes after oral treatment with 3 and 6 g (Cmax 0.9-1.0 µmol/ml and 0.6-2.2 µmol/ml, respectively). Plasma levels dropped quickly in three hours after treatment. At 10 g the maximum plasma level (0.9-2.2 µmol/ml) was reached after 2-4 hours and afterwards the decrease was more gradually compared to the lower dose levels (with a plateau phase) (ref. 48).

In healthy humans uptakes of 200 mg and 2g gave average C_{max}, T_{max} and $T_{1/2}$ of 3.3 and 42 µg/mL (0.027 and 0.34 µmol/ml), 0.3 and 0.5 h, and 0.6 and 3.5 h, respectively. The plasma concentration time (AUC) resulting from a 10 fold higher dose increased 62 fold (ref. 111).

Administration of nicotinamide in gelatin capsules (1, 3 or 6 g) to healthy volunteers gave plasma peak levels within 45 minutes after administration. The peak concentration and the elimination half-life were related to the dose administered, the latter, however increased non-linear with the dose, indicating a suturable metabolism (ref. 63).

Conclusion: In general in humans plasma peak concentration (C_{max}) and the elimination half-life ($T_{1/2}$) of nicotinamide were related to the administered dose, whereas the peak time (T_{max}) was not strongly correlated to the dosage. The data indicate that the metabolic clearance pathways of nicotinamide are saturated at pharmacological doses.

3.1.2 Acute Toxicity

Studies in Animals

Oral

Two acute oral studies in rats were available yielding slightly different results. In the first study an LD_{50} value of about 3.5 g/kg bw was reported for both male and female animals. Effects were tremor and convulsions, sedation, and coma (ref. 9). In the other study a value of 7.1 g/kg bw was found for males and 5.5 g/kg bw for females. Clinical symptoms included ruffled coat, lethargy and coma (ref. 10). The oral LD_{50} in mice reported in a study was 3.1 g/kg bw. Loss of activity was observed in high dose animals within 60 minutes after dosing. Survivors were asymptomatic within 24 hours (ref. 11). Other data from the literature for nicotinamide administrated orally to mice and rats indicated LD_{50} values between 2.0 and 3.0 g/kg (ref. 11, 96).

Dermal

Acute dermal toxicity was established in rabbits (ref. 12). When applied via this route an LD_{50} of >2000 mg/kg bw was found for nicotinamide.

Inhalation

No data.

Other Routes of Exposure

Other published data indicated intraperitoneal and intravenous LD_{50} values in mice between 1600 and 2600 mg/kg bw (ref. 35, 39, 53).

Studies in Humans

In a study with 6 volunteers (single dose between 3 and 9 g/day) toxic symptoms associated with nicotinamide were mild and consisted mainly of nausea (ref. 92).

Conclusion

Nicotinamide is of very low acute toxicity to mammals. The acute oral LD_{50} value derived from studies in experimental animals is 3500 mg/kg bw. For acute dermal toxicity a single LD_{50} of >2,000 mg/kg bw is available.

3.1.3 Irritation

Skin Irritation

Studies in Animals

Nicotinamide, when applied under occlusion for 4 hours was not irritating to the rabbit's skin. In one animal slight erythema was seen 1 hour after removal of the patch (ref. 17). Exposure under occlusion can be regarded as a worst-case scenario.

Conclusion: No indication for irritation after contact with the skin.

Eye Irritation

Application of 0.1 g nicotinamide to the eyes of 3 rabbits induced irritation in two of the animals, which was reversible within 7 days. The third animal showed irritation after 2 hours and was killed for humane reasons (ref. 18). In a second study with a similar design irritant effects were reversible within one week except for hyperaemia of the conjunctivae in one animal (ref. 19)

Conclusion: Based on the available data nicotinamide is considered to be irritating to the eyes.

3.1.4 Sensitisation

Studies in Animals

Two studies on dermal sensitisation in animals are available. In a guinea pig maximisation test slight skin reactions were observed at the challenge in 4 of 20 test animals and 0 of 10 control animals. Therefore, it was concluded that this test was negative(ref. 114). The result was acknowledged by the results of a Buehler test, which was performed on 10 treated animals and 5 controls. None of the tested animals showed sensitisation (ref. 115).

Studies in Humans

A survey of the database of the dermatological hospitals in Germany revealed no cases of sensitisation to nicotinamide in over 50,000 patients registered in the database. In addition an extensive literature search did not yield any results (ref. 116).

Conclusion

Based on the results of animal testing and the fact that nicotinamide is handled in nearly every feed mill and it is a component of most shampoos, it can be concluded that the substance is not likely to have sensitising potential in humans.

3.1.5 Repeated Dose Toxicity

Studies in Animals

Oral

In a 4-week oral toxicity study 5 rats/sex/treatment received 0, 215 and 1000 mg nicotinamide/kg bw/d by gavage (ref. 13). Two additional groups of 5 rats, treated with 0 and 1000 mg/kg bw/d, were included in the study design and were allowed to recover for a 6 week period. In treated males body weight gain and food consumption were significantly decreased during part of the treatment period. Liver weight was increased in all treated animals. This finding was accompanied histopathologically by mild liver centrilobular hypertrophy. These effects were considered to be an adaptive response to nicotinamide treatment in males. In females at the high dose group

extramedullary haematopoiesis of the spleen was reported. The NOAEL derived from this study is 215 mg/kg bw/d.

In a dietary study administration of nicotinamide (35, 70 and 140 mg/kg bw/d) to male rats led to an enhanced growth at 70 mg/kg bw/d and growth inhibition at the highest dose level. No effects on weight of the adrenal glands and the kidney were seen. Relative liver weight was significantly decreased at 70 mg/kg bw/d only (ref. 61).

In another study male rats (10/treatment) were fed diets with high or low fat content with or without added nicotinamide (100 mg/kg bw per day) during 3 or 6 weeks. Increased concentrations of fat in the liver were found only when the high fat diet was combined with an excessive intake of nicotinamide. A further study suggested that the fatty livers resulted from an induced choline deficiency brought about by the methylation of nicotinamide to the excretory product N^1-methylnicotinamide (ref. 110). The toxicological relevance of the outcome of this study is doubted, as the study was not performed with a normal balanced diet.

Conclusion

The NOAEL after oral administration of nicotinamide is 215 mg/kg bw/d based on the minor effects on the liver and the spleen (females only)

Observations in Humans

An extensive literature is available concerning the effects of large doses (1 to 10 g daily) of nicotinamide administered for a few days to several years. The mostly cited side-effects such headache and nausea, vomiting, itching and insomnia were sporadic and transient. In two studies with 6 volunteers each, side effects such headache or nausea were observed in 3 cases at doses between 6 and 9 g/day (ref. 63, 92). In other studies with 10 patients each, individuals receiving 8-10 g nicotinamide daily showed severe nausea and vomiting, whereas lower dosages (3-6g) were well tolerated (ref. 48,64). In one study with 6 patients undergoing radiotherapy mild symptoms were seen at doses between 5 and 6 g/day (ref. 92). In another study with 40 head and neck cancer patients treated with 5-6 g/day nausea with or without vomiting occurred in 65% of the patients (ref. 69).

Minor abnormalities of liver enzymes can infrequently occur at the doses used for diabetes prevention. (ref. 119). In studies with diabetic and at-risk-of-diabetes patients who were treated for several years with 1.5 to 3 g nicotiniamide daily (25 and 42 mg/kg/day, respectively) no effect on a range of biochemical parameters including liver and kidney function tests was observed (ref. 120, 121).

Liver effects were also reported in a single case study at 9 g/day (ref. 101) and in a review of 1953 (ref. 39).

Conclusion

From the above, it can be concluded that side effects are generally seen after doses in excess of 6 g/day.

3.1.6 Mutagenicity

In vitro Studies

Nicotinamide was negative in an Ames test performed with Salmonella strains TA98, TA100, TA1535, TA1537 and TA1538 both with and without metabolic activation (rat S-9) (ref. 14). Other tests using Salmonella strains and liver S-9-mixes from rat, mouse or monkey showed a similar

result (ref. 25, 50, 65). One Ames test using TA97a and TA102 showed a weak, questionable response in the strain TA102 in absence of metabolic activation (ref. 51). Nicotinamide was not mutagenic in Saccharomyces stain D4 (ref. 25).

No chromosomal aberrations were observed in an adequate study according to the current standards with nicotinamide (ref.15). An older review article with limited information on the test design, however, indicated the presence of both structural and numerical aberrations (ref. 66).

Positive results have been reported in a number of studies to investigate sister chromatide exchange (SCE) induction (ref. 45, 76, 81 and 97), but these had limitations and activity was only seen at excessively high concentrations (15 mM or more) in the most reliable study Furthermore it has been suggested that such effects may be due to the ability of nicotinamide to inhibit poly (ADP) ribose transferase, an enzyme involved in repair of DNA-strand-breaks (ref. 76, 81). No conclusions regarding mutagenicity of nicotinamide can be drawn from these studies.

In vivo Studies

Two independent micronucleus tests (according to OECD 474) were performed with i.p. administration to male and female mice (ref. 16). No increased incidence of micronucleated erythrocytes was found in both tests, except for a slightly increased incidence in males treated at 1000 mg/kg bw in the first test scarified after 48 hours. Therefore, it can be concluded that nicotinamide is not clastogenic in this assay.

Conclusion

Nicotinamide is considered to be not mutagenic in bacteria. The substance did not induce clastogenic effects both *in vitro* and *in vivo*.

3.1.7 Carcinogenicity

In a lifetime carcinogenicity study in Swiss mice receiving 1% nicotinamide in the diet, no increase of tumour incidence was observed (ref 94).

In a few studies where nicotinamide was given in combination with known carcinogens, both promoting and antitumorigenic effects were reported (ref. 83, 87). Nicotinamide appeared to have a promoting effect in rats on pancreatic islet tumours when combined with streptzotocin (ref. 83) and on renal tumours in rats that were pre-treated with diethylnitrosamine (ref. 85). Urethane initiated lung tumorgenesis in mice was significantly inhibited by post-treatment with nicotinamide in the diet (1 and 2.5%) (ref. 55). The induction of pancreatic ductular adenomas and carcinomas induced by N-nitrosobis(2-oxoprolylamine) in hamster was completely inhibited by nicotinamide given intraperitoneally at 350 mg/kg (ref. 113).

3.1.8 Toxicity for Reproduction

Effects on Fertility

No data are available for fertility, but the available repeated dose toxicity studies did not give any indication for effects on the gonads (ref. 13).

Developmental Toxicity

A study on potential teratogenic effects is available with nicotinic acid but not with nicotinamide. Pregnant rats were exposed orally to 0, 40, 200 and 1000 mg/kg nicotinic acid during day 6-15 of gestation. They were sacrificed on day 20 and their reproductive tract was examined. Body weight gain of the dams in the highest dose group was slightly decreased. Placental weight was

significantly decreased at this dose level. Foetuses did not show any adverse effects, except for a significantly lower body weight in male offspring of females treated at 1000 mg/kg bw/d (ref. 20). There was no teratogenic effect up to the maximum dose of 1000 mg/kg bw/d. The NOAEL for maternal toxicity and foetal effects was 200 mg/kg bw/d. Effects at the higher dose level were related to maternal toxicity.

In rat the kinetics of nicotinic acid and nicotinamide are considered to be similar, as nicotinamide is deamidated to nicotinic acid to a large extent by micro-organisms in the gut. Hence, nicotinamide is expected to be absorbed as nicotinic acid mainly (ref. 103). Both nicotinic acid and nicotinamide are linked in the same physiological pathway of NAD synthesis.

Therefore it can be reasonably assumed that the study with nicotinic acid is relevant for the assessment of potential developmental effects after nicotinamide administration.

In mice nicotinamide was found to pass the placenta after intra peritoneal injection and suppressed significantly urethane-induced foetal malformations both after i.p. and dietary administration. Experiments without urethane, however, showed no consistent antiteratogenic potential on the high incidence of spontaneous malformations typical for the mouse strain used (CL/Fr) (ref. 55).

Conclusion

It can be concluded that effects of nicotinic acid on reproductive parameters were only present at maternal toxic doses. There was no evidence of teratogenicity. The NOAEL for developmental toxicity is 200 mg/kg bw/d (198 mg/kg bw/d for nicotinamide).

3.2 Initial Assessment for Human Health

Nicotinamide is a vitamin, an essential constituent for the synthesis of pyridine coenzymes in mammalian systems. The substance can be synthetised directly in the body from the aminoacid tryptophan. In humans exogeneous nicotinamide is easily absorbed from the gastro-intestinal tract. In other species it may be deamidated to nicotinic acid by intestinal micro-organisms before entering the systemic circulation. The substance can be incorporated into NAD(P) either directly or after deamidation or metabolised and excreted in urine. The primary metabolite in both humans and rats is N-methylnicotinamide.

The acute toxicity of nicotinamide after oral administration or dermal application is very low: oral LD_{50} 3-7 g/kg bw in rodents and dermal LD_{50} >2000 mg/kg bw in rabbits. Skin irritation studies indicate that nicotinamide has no potential to irritate the skin. Nicotinamide is an eye irritant. Evidence from human exposure indicates that nicotinamide is not a skin sensitiser.

In a 4-week oral toxicity study male rats dosed with 215 and 1000 mg/kg bw showed a significant decrease in body weight gain and food consumption during part of the treatment period. Liver weight was increased accompanied histopathologically by mild liver centrilobular hypertrophy in all treated animals. These effects were considered to be an adaptive response to nicotinamide treatment. In females at the high dose group extramedullary haematopoiesis was reported. The NOAEL derived from this study is 215 mg/kg bw. In this study no effects on male and female gonads were found.

A developmental toxicity test was performed in rats with nicotinic acid, which has a similar physiological function as nicotinamide and comparable kinetics as nicotinamide in rats. The NOAEL for maternal toxicity derived from this study was 200 mg/kg bw/d based on effects on body weight (equivalent to 198 mg/kg bw/d for nicotinamide). The NOAEL on reproduction toxicity and developmental toxicity is 200 mg/kg bw/d (equivalent to 198 mg/kg bw/d

nicotinamide) based on the significantly decreased placental and pup body weight (males only). No teratogenic effects were observed.

Nicotinamide is considered not mutagenic in bacterial strains. No chromosomal effects in mammalian cells were reported. In an *in vivo* micronucleus test no clastogenic effects were seen. Thus nicotinamide is not mutagenic.

In humans nausea with or without vomiting was the main effect after acute exposure and generally seen after doses in excess of 5 g/day. No persisting effects were reported.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Data are available on the acute toxicity of nicotinamide to fish, daphnia, algae and micro organisms.

4.1.1 Fish and invertebrates

In a 96-hours static fish toxicity test with *Poecilia reticulata* (ref. 5) according to OECD 203, no mortality or other effects of nicotinamide were reported. The 96-h LC_{50} was >1000 mg/L).

To Daphnia magna nicotinamide did not induce any effects at concentrations up to 1000 mg/L. Two separate tests (both static) were performed: one at concentrations between 100 and 1000 mg/L and another at 1000 mg/L only. The 24-h EC_{50} was >1000 mg/L.

A QSAR prediction (input CAS number) for the LC_{50}/EC_{50} for fish and daphnia using the ECOSAR programme (v0.99g) gave the following results:

Fish	96-hr LC_{50}	18189 mg/L
Daphnid	48-hr EC_{50}	16456 mg/L

Conclusions: Nicotinamide is of low acute toxicity to fish and aquatic invertebrates. LC_{50}/EC_{50} values are all in excess of 1000 mg/L.

4.1.2 Algae

For algae a 72-hours study with *Scenedesmus subspicatus* was available with virtually no growth in the first 24 hours of the study. The EC_{50} of >1000 mg/L derived in this study is based on both reduction of growth rate and biomass during the exponential growth phase (24-72 hours) of the study (ref. 7).

The findings in this test are supported by a QSAR prediction (input CAS number) for the 96-hour EC_{50} for algae of 8934 mg/L

Conclusions: Nicotinamide is of low acute toxicity to algae with an EC_{50} value in excess of 1000 mg/L.

4.1.3 Microorganisms

A 18-hour toxicity test on Pseudomonas putida gave an EC_{10} of 4235 mg/L (ref. 8). It cannot be excluded that the growth in controls during the test was sub-optimal.

Conclusions: Nicotinamide is of low toxicity to micro organisms with an EC_{10} value of 4235 mg/L.

4.1.4 Other

No data

4.1.5 Determination of PNEC aqua

Data are available from short term tests at 3 trophic levels. These data are in good agreement among species. Based on the values found (LC_{50}/EC_{50} >1000 mg/L) and applying an assessment factor of 100 in accordance with the OECD guidance the resultant $PNEC_{aqua}$ is >10 mg/L.

Conclusions: Nicotinamide is of low hazard to the aquatic environment with a tentative $PNEC_{aqua}$ of >10 mg/L.

4.2 Terrestrial Effects

No data available.

4.3 Other Environmental Effects

Based on the very low log K_{ow} of –0.38, nicotinamide is not expected to accumulate (BCF of 3.162).

4.4 Initial Assessment for the Environment

Nicotinamide is a solid with a vapour pressure of 31.4 hPa (at 25ºC), a water solubility of 691-1000 g/L and a Log K_{ow} of -0.38 (at 22°C). It has a calculated half-life for photo-oxidation of 2.23 days in the atmosphere. Nicotinamide will partition primarily to water (Mackay level III modelling). No hydrolysis is expected based on the stability of the amide bond. Nicotinamide is readily biodegradable (100% within one week). Based on the log K_{ow} nicotinamide is not expected to bioaccumulate (calculated BCF 3.162). It has a low potential for sorption to soil (predicted log Koc 0.97).

The 96-hour LC_{50} in fish for nicotinamide is >1000 mg/L The 24-hour EC_{50} for daphnia is >1000 mg/L. In a test with algae (*Scenedesmus subspicatus*, 72-hours exposure) virtually no growth was seen during the first 24 hours. The 72-hour E_bC_{50} and E_rC_{50} were >1000 mg/L. The EC_{10} for the inhibition of micro-organisms is 4235 mg/L.

5 RECOMMENDATIONS

The chemical is currently of low priority for further work.

The chemical is currently of low priority for further work based on a low hazard potential. However it is noted that the substance is an eye irritant.

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ANNEX: SEARCH CRITERIA

The publications enclosed in the dossier were cited in the BIBRA Toxicity Profile of Niacinamide. A few additional references were from the internal Lonza bibliography.

In addition MEDLINE and TOXLINE were examined (nicotinamide or 98-92-0 and toxic?) over the period 1998-2002.

SIDS Dossier

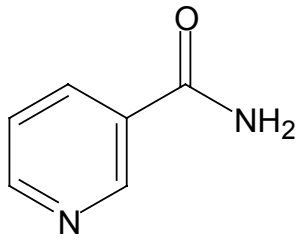
on the HPV Chemical

Nicotinamide

CAS no. 98-92-0

Substance Information

A.	CAS-number	98-92-0
B.	Name *(CAS name)*	3-Pyridinecarboxamide
C.	Name *(OECD name)*	Nicotinamide
E.	EINECS-Number	202-713-4
F.	Molecular Formula	$C_6H_6N_2O$
G.	Structural Formula	



J.	Molecular Weight	122.13
F.	Purity	≥ 99.0%

Introduction

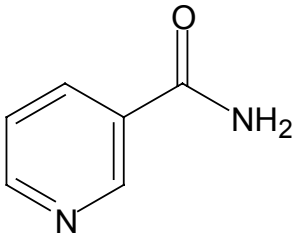
This report contains the (robust)summaries of the available data on nicotinamide for environmental fate, aquatic toxicity and human health effects.

The reports have been evaluated and assessed according to the Klimisch criteria (Klimisch et al., 1997). The following criteria can be distinguished, based on reliability, relevance and adequacy of the data
1 = Reliable without restriction
2 = Reliable with restrictions
3 = Not reliable
4 = Not assignable.

List of Abbreviations

[a]	Absolute to body weight
-	Absent
+	Present
ALAT	Alanine aminotransferase
ALP	Alkaline phosphatase
ASAT	Aspartate aminotransferase
AUC	Area under curve
C	Cornea
Ch	Chemosis
Conj	conjunctiva
d	Decrease
dc	Decrease (significant)
DEN	diethylnitrosamine
DMBA	9,10-dimethyl-1,2-benzanthracene
DOC	Dissolved Organic Carbon
DR	Dose-related
E	erythema
F	Female
FA	Fanconi's anemia
i	Increase
I	Iris
ic	Increase (significant)
M	Male
MI	Mitotic Index
MPCE	Micronucleated polychromatic erythrocytes
N/A	Not applicable
NCE	Normochromatic erythrocytes
nd	Not detectable
NMN	N'-methylnicotinamide
NNO	Nicotinamide N-oxide
O	Oedema
PCE	Polychromatic erythrocytes
2-PYR	N'-methyl-2-pyridone-5-carboxamide
QCs	Quality control samples
[r]	Relative to body weight
Red	redness
SGOT	Serum glutamic oxalacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TS	Test Substance
x	Yes

1.01. Chemical identity

CAS No.	:	98-92-0
OECD name	:	Nicotinamide
Chemical/IUPAC name	:	3-Pyridinecarboxamide
EINECS number	:	202-713-4
Molecular formula	:	$C_6H_6N_2O$
Molecular weight	:	122.13
Structural formula	:	

1.02. OECD information

Sponsor country	:	Switzerland
Lead organisation	:	Dr. Georg Karlaganis Swiss Agency for the Environment, Forests and Landscape CH-3003 Berne, Switzerland e-mail: georg.karlaganis@buwal.admin.ch
Name of responder (leader of consortium)	:	This substance is evaluated under the OECD HPV programme

1.1. General substance information

Type of substance	:	Organic
Physical state	:	Crystalline powder (Ref. 117)
Colour	:	White (Ref. 117)
Odour	:	Odourless (Ref. 117)
Purity	:	>99% (Ref. 117)

1.2. Impurities

No data

1.3. Additives

No data

1.4. Synonyms

Niacinamide, pyridine-3-carboxamide

1.5. Quantity

The worldwide production is estimated to amount to about 15'000 tonnes per year (data 2001). The total quantity annually produced or imported into Europe elevates to about 5'000 tonnes.
1.6. Use pattern

TYPE OF END USE	% OF PRODUCTION VOLUME	SPECIFIC APPLICATIONS
Dietary supplement, food	30%	Enrichment of various foods and drinks
	10%	In tablets and capsules
Dietary supplement, feed	50%	In poultry, swine, fish, dairy nutrition etc
Cosmetics	10%	Hair and skin conditioning agent (Weight fraction in products 0.002).
Therapeutics	negligible	Treatment of chronic alcoholism
		Animal pharmaceuticals (Weight fraction in products 0.001)
		Other, for research only

1.7. Sources of exposure

Environmental exposure via the aquatic route.

Consumer exposure via the dermal and oral route.

Worker exposure via the dermal and inhalatory (aerosol) route.

1.8. Additional information

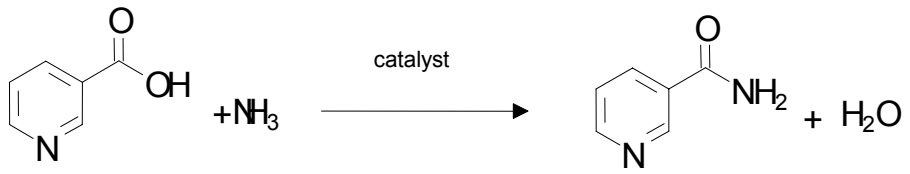
Manufacturing process

Nicotinamide can be synthesized industrially by two ways, either starting from nicotinic acid or starting from 3-cyanopyridine.

Description of the process starting from nicotinic acid

Nicotinic acid is melted and reacted with ammonia gas to yield nicotinamide. The reaction is catalyzed by the presence of ammonium salts. After distillation, nicotinamide is dissolved in water, purified by the addition of activated carbon, filtered, recrystallized and centrifuged. The nicotinamide contained in the mother liquor is reclaimed by a special recovery operation. The wet pure nicotinamide filter cake is dried under vacuum in a rotary vacuum drier.

Chemical reaction:



nicotinic acid ammonia nicotinamide water

Description of the process starting from 3-cyanopyridine

A buffered solution of 3-cyanopyridine in water is hydrolysed to nicotinamide in the presence of a catalyst. The resulting solution is purified over activated carbon, filtered and then concentrated in a evaporator. The concentrated nicotinamide solution is dried under vacuum.

Chemical reaction:

3-cyanopyridine water nicotinamide

2.1. Melting Point

Title	CRC Handbook of Chemistry and Physics.
Date of report	1999-2000
GLP	No.
Reference	1.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline	Not indicated.
Melting point	129-31 °C.
Reliability	4.

Title	Beilstein.
Date of report	1988-1999 CD ROM.
GLP	No.
Reference	2.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline	Not indicated.
Melting point	127-131 °C (mean of numerous studies).
Rev. note	A few lower values are also reported, probably from samples that were not pure enough or not dried well enough.
Reliability	4.

Title	Safety Data Sheet Niacinamide USP
Date of report	09-05-200
GLP	No.
Reference	117.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline	Not indicated.
Melting point	128-131 °C
Reliability	4.

Title	The Merck Index.
Date of report	2000 CD ROM.
GLP	No.
Reference	118.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline	Not indicated.
Melting point	128-131 °C
Reliability	4.

2.2. Boiling point

Title	CRC Handbook of Chemistry and Physics.
Date of report	1999-2000
GLP	No.
Reference	1.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline	Not indicated.
Boiling point	157 °C (at 0.066 Pa).
Reliability	4.

Title	Safety Data Sheet Niacinamide USP
Date of report	09-05-200
GLP	No.
Reference	117.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline	Not indicated.

Boiling point 224 °C (at 2000 Pa).
Reliability 4.

2.3. Density

Title CRC Handbook of Chemistry and Physics.
Date of report 1999-2000
GLP No.
Reference 1.
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline Not indicated.
Density 1.4 g/cm^3 (25°C)
Reliability 4.

Title Safety Data Sheet Niacinamide USP
Date of report 09-05-200
GLP No.
Reference 117.
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline Not indicated.
Density Ca. 500-700 kg/m^3 (bulk density)
Reliability 4.

2.4 Vapour Pressure

Title Beilstein.
Date of report 1988-1999 CD ROM.
GLP No.
Reference 2.
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline Not indicated.
Vapour pressure 31.4 hPa at 25 °C.
Huettenrauch, Die Pharmazie, , 37(10): 720-724, 1982 (ref. 122)
Reliability 4.

2.5 Partition Coefficient

Title Determination of the partition coefficient of P0080 (n-octanol/water).
Date of report December 5, 1990.
GLP Yes.
Reference 3.
Test substance CAS 98-92-0 (Nicotinamide), purity 99.9%.
Guideline OECD 107(1981); 84/449/EEC A8.
Procedure n-Octanol and water were saturated with each other by shaking for 24 hours and separated after 4 hours standing.
A stock solution with a concentration of 1000 µg/ml was prepared by weighing 100 mg of test substance into a 100 ml volumetric flask and filling up with water (n-octanol saturated; pH 6.1). 7.5, 10 and 5 ml of stock solution were put into 20 ml screw cap glass flasks (duplicates) and 7.5, 5 and 10 ml of n-octanol was added, respectively. The flasks were agitated on a laboratory shaker (150 rpm) for 30 minutes at ~ 22 °C, whereafter the samples were centrifuged (3000 rpm) for 15 minutes. The pH of the aqueous layer was measured to be 6.4. 250-500 µl of each phase was diluted with mobile phase and analysed by HPLC/UV (220 nm).
Results Analytical method is acceptable (r^2 = 0.99), QCs showed recoveries of 96-104% and were fortified at 50 µg/mL (n-octanol) and 1000 µg/mL (water).

treatment	**1a**	**1b**	**2a**	**2b**	**3a**	**3b**
amount of test substance [mg]	7.5	7.5	10	10	5	5

volume of octanol (ml)	7.5	7.5	5	5	10	10
volume of water (ml)	7.5	7.5	10	10	5	5
concentration in octanol phase [µg/mL]	295	306	349	370	210	209
concentration in aqueous phase [µg/mL]	697	677	802	792	553	557
recovery [%]	99	98	98	98	97	97
Pow	0.42	0.45	0.44	0.47	0.38	0.38
average Pow±SD	0.42 ± 0.03					
10log(Pow)	-0.38					

Conclusion ^{10}log(Pow) –0.38.
Rev. note No remarks.
Reliability 1.

2.6. Water Solubility and Dissociation Constant

Title The Merck Index
Date of report 2000 CD ROM.
GLP No.
Reference 118.
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline Not indicated.
Water Solubility 1 g/mL
Dissociation Constant 3.3 (20 °C)
Reliability 4.

Title Safety Data Sheet Niacinamide USP
Date of report 09-05-200
GLP No.
Reference 117.
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline Not indicated.
Water Solubility 691 g/L (20 °C)
Ethanol Solubility 660 g/L
Reliability 4.

Title Data from SRC PhysProp Database
Date of report 2002
GLP No.
Reference SRC PhysProp Database
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline Not indicated
pKa 3.35
Reliability 2

Title -
Date of report 2002
GLP No.
Reference Pallas 2.1
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline Not indicated
Method Calculation
pKa 3.65
Reliability 2

3.1. Stability

A Photodegradation

Reference	Epiwin vs 3.10
Test substance	CAS 98-92-0 (Nicotinamide)
Test method	SMILES : O=C(N)c(cccn1)c1 CHEM : 3-Pyridinecarboxamide MOL FOR: C6 H6 N2 O1 MOL WT : 122.13
Result	---------- SUMMARY (AOP v1.90): HYDROXYL RADICALS ---------- Hydrogen Abstraction = 0.0000 E-12 cm3/molecule-sec Reaction with N, S and -OH = 2.0000 E-12 cm3/molecule-sec Addition to Triple Bonds = 0.0000 E-12 cm3/molecule-sec Addition to Olefinic Bonds = 0.0000 E-12 cm3/molecule-sec **Addition to Aromatic Rings = 0.3373 E-12 cm3/molecule-sec Addition to Fused Rings = 0.0000 E-12 cm3/molecule-sec OVERALL OH Rate Constant = 2.3373 E-12 cm3/molecule-sec HALF-LIFE = 4.576 Days (12-hr day; 1.5E6 OH/cm3) HALF-LIFE = 54.915 Hrs
Reliability	4

B Stability in Water

Reference	Epiwin vs 3.10
Test substance	CAS 98-92-0 (Nicotinamide)
Test method	HYDROWIN Program (v1.67) Results: SMILES : O=C(N)c(cccn1)c1 CHEM : 3-Pyridinecarboxamide MOL FOR: C6 H6 N2 O1 MOL WT : 122.13
Result	AMIDE: -N-C(=O)-C- Compound has an amide group; C=O located at SMILES atom #: 2 Hydrolysis Rate Extremely Slow or t1/2 > 1 Year
Reliability	4

C Stability in Soil

No data

3.2. Monitoring Data

3.3.1. Transport and Distribution between Environmental compartments

Reference	Epiwin vs 3.10
Test substance	CAS 98-92-0 (Nicotinamide)
Test method	Level III Fugacity Model (Full-Output): ========== Chem Name : 3-Pyridinecarboxamide Molecular Wt: 122.13 Henry's LC : 2.9e-012 atm-m3/mole (Henrywin program) Vapor Press : 0.000198 mm Hg (Mpbpwin program) Liquid VP : 0.00108 mm Hg (super-cooled) Melting Pt : 99.4 deg C (Mpbpwin program) Log Kow : -0.37 (Kowwin program) Soil Koc : 0.175 (calc by model)

Result

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	3.52e-012	110	0
Water	99.8	900	1000
Soil	1.67e-006	900	0
Sediment	0.185	3.6e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	3.98e-023	1.26e-010	1.99e-010	1.26e-011	1.99e-011
Water	6.71e-017	435	565	43.5	56.5
Soil	4.11e-023	7.3e-006	0	7.3e-007	0
Sediment	6.18e-017	0.201	0.0209	0.0201	0.00209

Persistence Time: 566 hr
Reaction Time: 1.3e+003 hr
Advection Time: 1e+003 hr
Percent Reacted: 43.5
Percent Advected: 56.5

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 109.8
Water: 900
Soil: 900
Sediment: 3600
Biowin estimate: 2.661 (weeks-months)

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004)

Reliability 4

3.3.2. Distribution

Reference Epiwin vs 3.10
Test substance CAS 98-92-0 (Nicotinamide)
Test method PCKOCWIN v1.66
Result Koc = 1.7123
Rev note The Koc of this structure may be sensitive to pH! The estimated Koc represents a best-fit to the majority of experimental values; however, the Koc may vary significantly with pH
Reliability 4

Reference TGD part III
Test substance CAS 98-92-0 (Nicotinamide)
Test method LogKoc = 0.52 logKow + 1.02 (non-hydrophobes)
Log Koc = 0.33 logKow + 1.25 (amides)

Result Mean Koc 0.97
Reliability 4

Reference EUSES
Test substance CAS 98-92-0 (Nicotinamide)
Test method SimpleTreat model

Vapour pressure	31.4 hPa
Solubility	691000 mg/L

	Log Kow	-0.38
	Log Koc	0.97
	Biodegradability	Ready biodegradable
Result	Fraction degraded [%}	87.2
	Fraction to air [%]	0.24
	Fraction to water [%]	12.6
	Fraction to sludge [%]	0.009
Reliability	4	

3.4. Biodegradation

Title Ready biodegradability: “Modified OECD screening test” for P0080
Date of report October 12, 1990.
GLP Yes.
Reference 4.
Test substance CAS 98-92-0 (Nicotinamide), purity 99.9%.
Test method 84/449/EEC, C.3. (1985); OECD 301 E (1981).
Procedure Aliquots of a stock solution of the test substance (tested conc. 34 and 36 mg/l ⇔ 20.5 and 18.7 mg DOC/l), inoculum from a domestic sewage plant (source: Ara Sissach, Switzerland; washed 3 times with tap water before usage; final test conc. 0.5 ml/l) and nutrient solution were mixed. Water was added to give a total volume of 1 litre. 30 ml of test medium in 50 ml conical flasks were shaken in the dark. Duplicate test mixtures for each concentration were incubated at 20.6-22°C for 28 days. The following controls were included:
Control without test substance but with inoculum (blank, 1 flask).
Positive control, aniline (15.8 and 17.3 mg DOC/l) with inoculum (2 flasks per concentration).

Duplicate aliquots were removed from each flask on day 0, 7, 14, 21, 27 and 28, centrifuged and analysed for DOC using a carbon analyser.

Findings

	% DOC removal [% of day 0 values (corrected for blank)]	
day	**P0080 with inoculum**	**Aniline**
0	0	0
7	100	99
14	101	96
21	94	91
27	96	96
28	96	95

Conclusion Readily biodegradable.
Rev. note The pH of the test solutions was not measured.
The amount of ammonium chloride in the stock solution was 20.0 g instead of the 0.5 g recommended in the OECD 301E guideline; this has no effect on the study reliability.
Reliability 1.

4.1. Acute Toxicity to Fish

Title	96-hour acute toxicity study in the guppy with nicotinamide.	
Date of report	July 23, 1990.	
GLP	Yes.	
Reference	5.	
Test substance	CAS 98-92-0 (Nicotinamide), purity >99%.	
Test method	EEC directive 84/449, C-1 (1984); OECD 203 (1984).	
Stat. method	Not applicable.	
Test system	**Species**	Guppy (Poecilia reticulata, Teleostei Poeciliidae), 1.5 and 2.5 weeks old.
	No. of fish	10/vessel, 3 vessels/treatment and 1 vessel/control.
	Concentrations	Nominal: 0,1000 mg/l.
	Test conditions	96-h static test in 1 L glass vessels containing test medium (hardness 201 mg/l $CaCO_3$, pH 8.2±0.2); 16 h light, unfed (24 h prior to and during test).
	Analysis	Analyses at 0, 24 and 96 h in an extra vessel without fish by HPLC with UV-detection at 260 nm.
	Phys. meas.	Daily for all vessels for pH (7.8-8.2) and O_2 >80%; temperature daily in one control vessel (22-23°C).
	Observations	Mortality/symptoms at 4, 24, 48, 72 and 96 h.
Results	**Analytical**	Mean measured concentration 96-99% of nominal.
	Biological	No mortality or any other effects were observed in this limit test.
Conclusion	96-h LC50 > 1000 mg/l.	
Rev. note	No information on the length and weight of the fish used (OECD 203: 20±10 mm, loading 1 g fish/l) is available. The fish could be smaller than recommended, based on the age of the fish (only 1.5-2.5 weeks). In a range-finding test no mortality was seen at concentrations of 0.1 to 1000 mg/l. A reference test with pentachlorophenol (performed two weeks earlier) at concentrations of 0.18, 0.32, 0.56, 1.0 and 1.8 mg/l resulted in a 96h-LC50 between 0.56 and 1.0 mg/l indicating an accurate sensitivity of the test system.	
Reliability	1.	

4.2. Acute Toxicity to Aquatic Invertebrates

Title	Acute toxicity study in Daphnia magna with nicotinamide.	
Date of report	July 5, 1990.	
GLP	Yes.	
Reference	6.	
Test substance	CAS 98-92-0 (Nicotinamide), purity >99%.	
Test method	EEC directive 84/449, C-2 (1984); OECD 202 (1984).	
Stat. method	None.	
Test system A	**Species**	*Daphnia magna*, <24 h old.
	No. of daphnids	10/beaker, 2 beakers/treatment.
	Concentrations	Nominal: 0, 100, 180, 320, 560 and 1000 mg/L.
	Test conditions	Static for 24 hours in 250 mL glass vessels containing 100 mL of medium; 16 h light, unfed. Dilution water: Dutch tap water purified by reverse osmosis. Chemistry: hardness 201 mg/L ($CaCO_3$); Ca/Mg ratio: 3.1; Na/K ratio: 3.5 and pH 8.2±0.2.
	Analysis	No analyses performed.
	Phys. meas.	At beginning and end of test: overall range pH 8.1-8.2 and O_2 97-112% (for all concentrations and control); temperature 18.5-20°C (in one control vessel).
	Observations	Immobility at 24 h.
Results	**Biological**	No immobility.
Test system B	**Species**	*Daphnia magna*, <24 h old.
	No. of daphnids	10/beaker, 4 beakers/treatment; 2 beakers as control.
	Concentrations	Nominal: 1000 mg/L.

	Test conditions	Static for 24 hours in 250 mL glass vessels containing 100 mL of medium; 16 h light, unfed. Dilution water: Dutch tap water purified by reverse osmosis. Chemistry: hardness 201 mg/L ($CaCO_3$); Ca/Mg ratio: 3.1; Na/K ratio: 3.5 and pH 8.2±0.2.
	Analysis	No analyses performed.
	Phys. meas.	At beginning and end of test: overall range pH 8.2-8.3 and O_2 97-110% (for all concentrations and control); temperature 19-19.5°C (in one control vessel).
	Observations	Immobility at 24 h.
Results	**Biological**	No immobility.
Conclusions	24-h EC_{50} > 1000 mg/L .	
Rev. note	1. No analyses to confirm the nominal concentrations were performed. However, OECD 202 does not require analytical confirmation of the test compound and the solubility is about 1 kg/L, so the study reliability was not lowered. 2. In test A no immobility was found which was contrary to findings of the range finding test (90% inhibition at 1000 mg/L); therefore, a second test B – a limit test – was performed. 3. A 48-h reference test with potassium dichromate was included (performed 6-8 March, 1990). The 24h-EC50 was 1.57 mg/L.	
Reliability	1.	

4.3. Toxicity to Aquatic Plants e.g. Algae

Title	*Scenedesmus subspicatus,* fresh water algal growth inhibition test with nicotinamide.	
Date of report	September 10, 1990.	
GLP	Yes.	
Reference	7.	
Test substance	CAS 98-92-0 (Nicotinamide), purity >99%.	
Guideline	OECD 201 (1984); EEC directive 67/548 (amended 87/302).	
Stat. method	None.	
Test system	**Species**	*Scenedesmus subspicatus*, strain: CCAP 276/20.
	Initial cell conc.	$2*10^4$ cells/mL.
	No. of replicates	3 per treatment, 6 for controls.
	Concentrations	Nominal 100, 180, 320, 560 and 1000 mg/L, untreated controls.
	Test conditions	72-h static test in 250 ml glass vessels containing 300 ml algal medium (in accordance with OECD 201) with continuous illumination (6000-8000 lux).
	Analysis	Not performed.
	Phys. meas.	pH. At 0 and 72 h in test solutions and untreated controls 8.1-9.9. Temperature. 21.5-25.5°C.
	Observations	Cell density at 0, 24, 48 and 72 h by spectrophotometry.

Results

For biological data see table below.

Biological results

		Nominal concentration [mg/L]					
Parameter	**Time [h]**	**0**	**100**	**180**	**320**	**560**	**1000**
Mean cell density [10^4 cells/ml]	0	2	2	2	2	2	2
	24	2	2	2	2	2	2
	48	24.9	26.3	28.6	26.3	26.6	20.6
	72	126	158	141	149	162	105
Inhibition [%] – AUC	0-72	0	-21	-14	-15	-23	17
Inhibition [%] – growth rate	0-72	0	-5	-3	-4	-6	4

Conclusions	72 h-EC_{50} >1000 mg/L (see rev.note 3)
Rev. note	1. Strong rises in pH were recorded. Such rises are often associated with strong cell growth, probably due to CO_2 depletion from test media. In the present test the flasks were shaken. Since the control was not affected by lack of CO_2 (a very adequate growth factor of 63 in 48 hours was measured.

	2. The final test volume of 300 ml exceeds the 250 ml of the test vessel. 3. Because no growth was observed during the first 24 hours, the test should have been extended with another 24 hours. Actually, the EC50 measured is a 48 h EC50 and not a 72 h EC50 as reported in the report. Therefore, the reliability is lowered. 4. The nominal 96 h EC50 of potassium dichromate for growth inhibition lay between 0.32-1.0 mg/L.
Reliability	2.

4.4. Toxicity to Bacteria

Title	Acute bacteria cell multiplication inhibition test with Nicotinamide
Date of report	1990.
GLP	Yes.
Reference	8.
Test substance	CAS 98-92-0 (Nicotinamide), purity >99%.
Test method	Umweltsbundesamt (UBA) Guidelines: Bewertung wassergefaehrdender Stoffe, III Bestimmung der akuten Bakterientoxizitaet, Ad-hoc-Arbeidsgruppe I (Obmann Dr. Niemitz), LTwS, Nr. September 1979.
Procedure	A stock solution of nicotinamide was prepared in water (conc. 10 g/l, pH 6.9). Test solutions (100 mL) were prepared by adding together the required volume of stock solution, nutrient medium, water and 10 ml of inoculum of *Pseudomonas putida.* Test concentrations were 3.9, 7.8, 15.6, 31.3, 62.5, 125, 250, 500, 1000, 2000, 4000 and 8000 mg/L. Three parallel series of 12 flasks for each concentration, 10 blank flasks (without test substance), 12 abiotic control flasks (without inoculum) and positive control (5 flasks (pH 7.1): 3950, 7900, 15800, 31600, 63200 mg methanol/L) were incubated for 18±2 h at 25°C. At the end of the test, the extinction (436 nm) was measured.
Results	Inhibition [%] at 3.9-4000 mg/L ≤3% and at 8000 mg/L 48% Reference substance: EC_{10} 7944 mg/L.
Conclusion	18-h EC_{10} 4235 mg/L.
Rev. note	There was no information on the pH during the test, the test medium used differed slightly from the medium described in DIN 38412 Teil 8 The growth factor could not be deduced from the report (DIN 38 412 Teil 8: 100 after 18 h). The positive control was reported to fall within the expected range (historical control). The study reliability was lowered, because it cannot be excluded that the growth factor was sub-optimal (DIN 38412 Teil 8).
Reliability	2.

5.1. Pharmacokinetics

Title	Niacin (vitamin B3)
Date of report	1996.
GLP	Not applicable.
Reference	33.
Test substance	Not applicable.
Guideline	Not applicable.
Stat. method	Not applicable.
Findings	Niacin includes two vitamers nicotinic acid and nicotinamide. Humans are able to synthesize nicotinic acid from tryptophan. Another source for nicotinic acid is the gut flora. In humans there is no deamidation of nicotinamide to nicotinic acid in the gut. Nicotinamide is rapidly absorbed in stomach and small intestine. In plasma both the acid and the amide form are found. Erythrocytes take up the acid by a sodium-dependent saturable transport system. Both the acid and the amide are able to pass the blood-brain barrier, however separate systems for uptake have been identified. Brain cells have a high affinity for nicotinamide, but not for nicotinic acid. Nicotinamide is the main substance that is transported between the different tissues as a precursor of NAD synthesis. The liver, kidneys, brain and erythrocytes prefer nicotinic acid as a precursor for NAD synthesis, but testes and ovaries prefer nicotinamide. NAD nucleosidase cleaves NAD with nicotinamide as one of the products. This can be deamidated to form nicotinic acid (and re-converted to NAD) or methylated and released via urine. Excretion of the amide (and its metabolites) tends to be more extensively compared to the acid.
Conclusion	In humans nicotinic acid and nicotinamide show differences with regard to absorption, transport, and metabolism.
Rev. note	Review article covering chemistry, sources, ADME, metabolic functions, deficiency and requirements.
Reliability	4

Title	Nicotinamide administration alters the activities of hepatic microsomal mixed function oxidases.
Date of report	1980.
Reference	34.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
GLP	No.
Method	Nicotinamide (1 g/kg b.w.) was administered intraperitoneally to male and female Wistar rats (150-200 g). 24 hours after administration, rats were sacrificed and liver microsomes were isolated for determination of liver enzyme activities.

Results

Enzyme	Males	Females
Cytochrome P450	dc	
Aniline hydroxylase	dc	ic
Aminopropyrine N-demethylase	dc	d
p-nitroanisole-O-demethylase	dc	ic
NADPH cytochrome-C reductase	dc	ic
Aryl hydrocarbon hydroxylase	ic	ic

Conclusion	No toxicity was observed in animals treated with nicotinamide.
Rev. note	Journal article. The effects show a strong influence of sex.
Klimsich criterium	4.

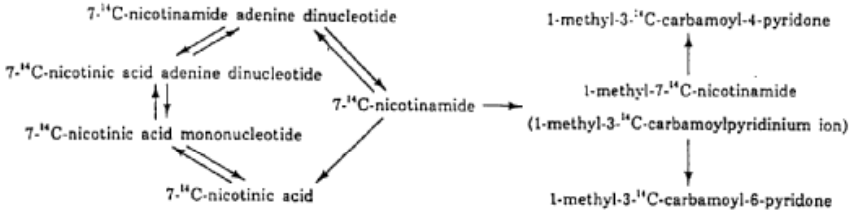
Title	Drug-biomolecule interactions: drug toxicity and vitamin coenzyme depletion.

Date of report 1975.
Reference 35.
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
GLP No.
Procedure Mice were injected i.p. with the LD_{25} dose (1940 mg/kg) of nicotinamide after pre-treatment with radioactively labelled nicotinic acid .
Results Nicotinamide administration resulted in a statistically significant increase of urinary ^{14}C (+42%) and in an altered disposition of endogenously liberated 7-^{14}C-nicotinamide).

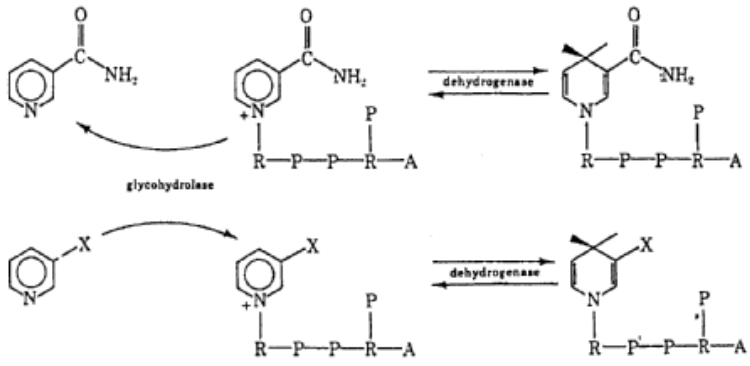
Percentage of total urinary radioactivity		
	Control	**Treated**
^{14}C-1-methylnicotinamide	32	11
^{14}C-nicotinic acid	7.4	10
^{14}C-pyridones	45	<1.0
^{14}C-nicotinamide	12	64

Tissue radioactivity x 10^{-3} (dpm/g)		
	Control	Treated
Brain	6.01	5.25
Lungs	13.0	8.53
Liver	4.46	4.27
Kidneys	18.72	10.35

Conclusion These results can be interpreted as the consequence of a competition between administered nicotinamide and endogenous 7-^{14}C-nicotinamide at the level of glycohydrolase, involving 7-^{14}C-nicotinamide-labeled endogenous NAD and the endogenous nicotinamide pool.
The metabolic pathways of nicotinamide are presented in the schemes below:



Scheme I—Biotransformation of 7-^{14}C-nicotinic acid and some urinary metabolites of 7-^{14}C-nicotinamide dinucleotide-derived 7-^{14}C-nicotinamide in the mouse



Scheme II—Illustration of the nicotinamide site of competitive antimetabolite (3-X-pyridine) incorporation into the nicotinamide dinucleotide pool

Rev. note Journal article.
The intraperitoneal route surpasses Nicotinamide metabolism by intestinal bacteria.

Reliability	4.

Title	Nicotinamide pharmacokinetics in patients.
Date of report	1995.
Reference	48.
Test substance	CAS 98-2-0 (Nicotinamide), 500 mg tablets, purity not indicated.
GLP	No.
Remark	The pharmacokinetics of nicotinamide were investigated in patients with superficial recurrent or metastatic cancer, undergoing combined nicotinamide, hyperthermia and radiotherapy treatment. Nicotinamide was administered orally at 3, 6 or 10 g (3 patients per treatment), the 3 g dose was increased on successive treatment days to 4, 5, and 6 g resp. Plasma nicotinamide levels were determined by HPLC at 0.5, 2, 3 and 4 h after administration. Plasma nicotinamide levels were dose dependent and showed linear relationship over the range studied. Maximums (up to 269 μg/mL) were attained at 30 min (average concentration of 156 μg/mL) for all but one dose, for 10 g the maximum level was reached at 2-4 hours. For dosed up to 6 g, levels dropped quickly in the 3 hours after the maximum dose (177 μg/mL) was reached. For higher doses a more gradual fall or plateau was observed. Patients on 10 g of nicotinamide showed severe nausea and vomiting within 30 min, to one hour after administration, lasting up to 24 h. At lower dosages nicotinamide was well tolerated.
Rev. note	The study was conducted with regard to sensitization effect in radiotherapy . Journal article
Reliability	2.

Title	Niacin and niacinamide
Date of report	1988.
GLP	Not applicable.
Reference	49.
Test substance	Not applicable.
Guideline	Not applicable.
Stat. method	Not applicable.
Findings	Niacin includes two vitamers nicotinic acid and nicotinamide. Both are absorbed in the small intestine by passive diffusion (or another not readily saturable process). The amide is absorbed more rapidly. Nicotinamide is the primary circulating form. Nicotinamide easily passes the blood brain barrier and is taken up by brain cells by a high affinity accumulation system. Main urinary metabolites of both vitamers are N^1-methyl-nicotinamide and 2-pyridone derivatives (N^1-methyl-2-pyridone-5-carboxyamide). Nicotinuric acid is found in urine after nicotinic acid administration, but also after large doses of nicotinamide (route probably via nicotinamide deaminase). Peak plasma levels are reached ½ - 2 hours after dosage for both substances. Nicotinamide can not be used in the treatment of elevated blood lipid levels. It is used in nutrient deficiency seen in alcoholics. In diabetes mellitus it slows down the destruction of pancreatic beta-cells. Other uses are in genetic disease related to tryptophan deficiency, in schizophrenia and depression. Nicotinamide is acutely more toxic than nicotinic acid, but in general it is well tolerated in patients. The side effects of nicotinic acid are not observed with nicotinamide.
Conclusion	Nicotinic acid and nicotinamide show differences with regard to absorption, use and toxic effects
Rev. note	Review article covering ADME, clinical studies, toxicity and interactions.
Reliability	4.

Title	Inhibiting effects of nicotinamide on urethane-induced malformations and tumors in

mice

Date of report 1988.

GLP No data.

Reference 55.

Test substance CAS 98-92-0, Nicotinamide ([carbonyl-^{14}C]nicotinamide), purity not indicated.

Guideline Not applicable.

Stat. method Not applicable.

Test system

Species	JCL:ICR mouse, age 8-10 weeks
No. of animals	Not indicated
Dosage	0.18 μCi ^{14}C-nicotinamide/g bw, i.p..
Procedures	Pregnant mice received a single dose of ^{14}C-nicotinamide on day 9 of gestation and were sacrificed 0.5, 1, 3, 6 and 12 hours after treatment. Specimens of maternal blood, lung, liver and placenta as well as foetuses were weighed and after solubilisation measured for radioactivity by LSC. Next to this procedure specimen were charged on paper to develop paper chromatography (isobutylic acid/NH_4OH/H_2O: 66/1.7/33) and radioactivity was measured by LSC.

Results

Specimen\time [h]	**Radioactivity (dpm/mg)**				
	0.5	**1**	**3**	**6**	**12**
Blood	50	40	20	30	20
Lung	400	350	500	300	250
Liver	600	850	600	500	400
Placenta	1700	1600	1000	750	300
Foetus	350	450	350	250	200

Most radioactivity corresponds to nicotinamide (all specimen), smaller amounts to NAD^+(all specimen) and $NADP^+$ (mainly in liver).

Conclusion Nicotinamide (and NAD^+) was found in foetuses

Rev. note No nicotinic acid was found in any of the specimen taken.

Reliability 2.

Title The inhibition of rat growth by nicotinamide.

Date of report 1942.

Reference 58.

Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.

GLP No.

Procedures Male rats (6/treatment, Vanderbilt strain, 48-52 g) were fed a low casein diet supplemented with 1% nicotinamide for 30 days (equivalent to a nicotinamide intake of 32 mg/day). N-methylnicotinamide excretion was investigated in 3 rats/treatment after 14 days on the experimental diet. Urine was collected during 3 days and analysed for total nicotinic acid and N-methylnicotinamide.
Male rats (6/treatment) received a 20% casein diet for 14 days, supplemented with 2% nicotinamide. Pooled urine samples were collected during the last two days of the experimental period.
Nicotinamide was supplemented to a 20% casein diet in various amounts (0.1-2.0%) and fed to rats (6 males/treatment) for 28 days.

Results Rats showed decreased body weight gain, decreased food intake, decreased liver weight and decreased percent liver fatty acids. Urine nicotinic acid was increased, as was abslolute N-methylnicotinamide excretion. Relative N-methylnicotinamide excretion was decreased. Recovery of nicotinamide was 33.8%.
Rats showed a sharp weight loss and decreased food intake. Liver weight was decreased, but liver fatty acid content was unaffected. Again, abslolute N-methylnicotinamide excretion was increased, but relative N-methylnicotinamide excretion was decreased. Nicotinamide recovery was 70%.
Growth rate decreased progressively with increasing nicotinamide supplementation, as did food intake. Liver fatty acid content showed an increase with nicotinamide supplementation up to 0.5% and a subsequent decrease towards normal levels with further increasing nicotinamide supplementation. Liver weight showed a dose dependent decrease.
Rev. note Journal article.
Reliability 4.

Title Nicotinamide pharmacokinetics in humans and mice: a comparative assessment and the implications for radiotherapy.
Date of report 1993.
Reference 63.
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
GLP No data.
Procedure In healthy human volunteers took nicotinamide doses up to 6 g in gelatine capsules. Plasma peak levels were measured from serial blood samples taken within 24 h. after administration of nicotinamide. Samples were analysed by HPLC/UV.
Mice were injected i.p. with 100-1000 mg/kg nicotinamide in 0.9% NaCl and a single blood sample was collected several times during 6 h after dosing.
Results Plasma peak levels for nicotinamide were attained in the human volunteers within 45 min. after ingestion. Peak plasma levels were dose dependent with a maximum of 160 µg/ml. Elimination half-life was also dose dependent, although not linear.
Mice injected with nicotinamide showed similar characteristics as the human data, although elimination half-lives were not dose dependent.
Side effects such headache, dizziness and nausea were mild and transient at 6 g..

	Dose (g)	Peak conc. (µg/ml)	T1/2 (h)	AUC (mg/ml x min.)
Human	1	21-36	1.1-3.8	3.2-5.3
	3	58-107	4.3-8.8	21.1-39.5
	6	120-190	6-11.5	78.7-132
Mouse	0.1	100	2.1	209

Rev. note Journal article.
Reliability 2.

Title Niacin
Date of report 1996.
GLP Not applicable.
Reference 67.
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline Not applicable.
Stat. method Not applicable.
Findings Nicotinamide is the major form of niacin (i.e. nicotinic acid and its derivatives exhibiting quantatively the biological activity of nicotinamide) in the bloodstream. Extracellular

nicotinamide regulates tissue concentrations of NAD. Excess plasma nicotinamide is mainly converted to storage NAD (not bound to enzymes) or to metabolites (methylation) that are excreted via urine.
Deamidation of nicotinamide may occur by intestinal microflora. Human tissue cells contain little nicotinamide deamidase.

Rev. note Review article covering chemistry, ADME, requirement , sources and deficiency, pharmacological effects and toxicity., The publication is a chapter of a book containing general information on niacin. In general the chapter discusses the formation of NAD and the part played by niacin and tryptophan in its formation.

Reliability 4.

Title Metabolic effects of nicotinamide administration in rats.
Date of report 1983.
GLP No data
Reference 71.
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline Not applicable.
Stat. method Student's t-test.
Test system
Species Rat (Sprague-Dawley), males, weight 70-80 g.
Source Simonsen Labs, Gilroy, CA.
No. of animals 6/ treatment (600 mg/kg bw: 11, controls 12)).
Dosage Daily i.p. injection for 5 weeks at 0, 60, 200 or 600 mg/kg bw in saline solution; Interim sacrifice after 2 weeks (5 animals at 600 mg/kg bw and 6 controls); Feed containing no choline and 12% casein ad libitum.
Observations Body weight/food consumption 3 times weekly; urine collection weekly (over 48 hours); blood collection, liver and kidney weight after 2 (interim sacrifice) and after 5 weeks
Parameters determined:
Urine: N^1-methyl-nicotinamide (NMN), N^1-methyl-2-pyridone-5-carboxamide (2-PYR) and creatinine
Liver: cystathionine γ-lyase activity (also in kidney), nicotinamide methyltransferase activity, total lipid level (gravimetrically).
Plasma and liver: choline levels
Blood: glucose and protein

Results

	Dose [mg/kg bw]				DR
Parameter	0	60	200	600	
Bodyweight gain		dc	dc	dc	X
Food consumption (A)		dc		dc	
Liver weight		ic^r	ic^r	ic^r	X
Kidney weight				ic^r	
Liver lipid (%)		ic	ic	ic	X
Urinary NMN (wk 0-5) (B)		i	i	i	X
Urinary 2-PYR (wk 0-5)	No treatment related effects				
Urinary creatinine	No treatment related effects				
Liver NMN		ic	ic	ic	X
Liver and kidney enzymes	No treatment related effects				
Liver choline		N/A	N/A	dc	
Plasma choline		N/A	N/A	d	
Bood glucose	No treatment related efects				

(A) food efficiency dose related decreased
(B) increased excretion with time

Conclusion N^1-methyl-nicotinamide (NMN) is the major metabolite of nicotinamide in rats

Rev. note It is reported that in humans N^1-methyl-2-pyridone-5-carboxamide (2-PYR) is the major metabolite excreted.
Methylation of nicotinamide may lead to methyl deficiency as reflected in the low tissue choline levels
Journal article.

Reliability 2.

Title The metabolism of high intakes of tryptophan, nicotinamide and nicotinic acid in the rat.

Date of report 1986.

GLP No data.

Reference 74.

Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.

Guideline Not applicable.

Stat. method Student's t-test.

Test system

Species: Rat (Wistar), males, age 3 weeks.

Source: Courtauld Institute of Biochemistry.

No. of animals: 5/ treatment.

Dosage: Single oral administration (gavage; 0.5 ml) of 1, 10, 100 mg nicotinamide /kg bw in 0.15 M NaCl to rats 3 weeks after weaning; control: 0.5 ml saline.
Dietary administration of 15 or 150 mg nicotinamide/kg feed for 3 weeks.

Observations: Amount of nicotinamide, nicotinic acid, N^1-methyl nicotinamide (NMN), methyl-2-pyridione-5-carboxamide (2-PYR), nicotinamide N-oxide (NNO) and nicotinuric acid by HPLC (detection 265 nm) in urine collected over 24 h separated in a neutral and acidic urine fraction. Total amount of nicotinamide nucleotides (NAD(P)) present in the liver was determined.

Results Mean values and standard deviations for 5 animals/group. LOD for nicotinamide = 1 pmol and for the other metabolites 0.5 pmol.

Test 1

Measurement\Dose	Control	1	10	100
Liver NAD(P) (nmol/g tissue)	367	412	430	503*
Nicotinamide(A)	0.8	1.1**	1.6**	41.4**
Nicotinic acid(A)	2.5	1.1*	1.6*	0.5**
NMN(A)	0.38	0.42	1.8*	12.2**
2-PYR(A)	0.61	0.88	4.1**	18.9**
NNO(A)	3.9	1.7**	2.2***	18.8**
Nicotinuric acid(A)	1.1	0.6***	0.7***	2.9**

(A) µmol/24 h
Significance: * 0.01>P>0.005, ** P<0.001, *** 0.005>P>0.001

Test 2

Measurement\Dose	15	150
Body weight (g)	101	103
Diet eaten (g/rat per 24 h)	10.3	10.4
Liver NAD(P) (nmol/g tissue)	78	125*
Nicotinamide(A)	0.7	1.2
Nicotinic acid(A)	nd	0.08
NMN(A)	0.2	1.4*
2-PYR(A)	0.2	1.5**
NNO(A)	1.0	0.9
Nicotinuric acid(A)	1.3	1.2

	(A) µmol/24 h nd = not detectable Significance: * 0.005>P>0.001, ** P<0.001	
Conclusion	Utilisation of nicotinamide for NAD(P) was limited. Excretion via methylated metabolites increased with increased dose, although the amount relative to the dose of nicotinamide decreased. Several unidentified peaks were present. Bacterial deamidation in the intestinal lumen seemed to be of minor importance, since urinary metabolism of nicotinic acid and nicotinamide were quantitatively different. Body weight decreased enormously after dietary nicotinamide intake due to low food intake; influence of the test substance cannot be excluded.	
Reliability	2.	
Title	Effect of nicotinamide administration to rats on the liver microsomal drug metabolizing enzymes.	
Date of report	1983.	
GLP	No data.	
Reference	80.	
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.	
Guideline	Not applicable.	
Stat. method	Not applicable.	
Test system	Species	Rat (Wistar), males.
	No. of animals	5/treatment.
	Experiment 1	*Dosage*: Single i.p. administration in physiological saline of 0, 100, 500 and 1000 mg/kg bw to rats, which were killed 24 hrs after injection. *Observations*: Amount of microsomal protein, hepatic NADPH-cytochrome *c* reductase activity and cytochrome P-450 activity were measured.
	Experiment 2	*Dosage*: i.p. administration of 0 or 500 mg nicotinamide /kg bw in physiological saline three times in every 7 hrs; the animals were killed 8 hours after the last injection. *Observations*: Total niacin per g liver, amount of microsomal protein and acitvities of cytochrome P-450, NADPH-cytochrome *c* reductase, aniline hydroxylase and aminopyrine N-demethylase.
	Experiment 3	*Dosage*: i.p. administration of 500 mg/kg bw nicotinamide suspended in corn oil twice at an interval of 10 hrs; a control group was used; the animals were killed 12 hrs after the second injection. *Observations*: As in experiment 2.
	Experiment 4	*Dosage*: A solution containing 1% nicotinamide, 5% sugar and 1% NaCl was given ad libitum iinstead of drinking water for 2 weeks; a control group was used. *Observations*: As in experiment 2.
Results	**Experiment 1**	Statistically significant increase of NADPH cytochrome *c* reductase activity at 500 mg/kw bw compared to control, but the activity was restored to the control level at 1000 mg/kg bw. No change in amount of cytochrome P-450 was observed. A dose-related total protein increase was seen.
	Experiment 2	Total amount of nicotinic acid in the liver had increased with 85%. The NADPH-cytochrome *c* reductase and aniline hydroxylase activities had increased with 77 and 66%, respectively. No effect was observed on the amount of microsomal protein, the amount of cytochrome P-450 and aminopyrine N-demethylase activity. Similar changes were observed 18 hrs after the last injection.
	Experiment 3	Increases in hepatic total amount of nicotinic acid, NADPH-cytochrome *c* reductase activity and aniline hydroxylase acitivity were observed of 162%, 244% and 70%, respectively. Other parameters measured were not affected.
	Experiment 4	The activities of NADPH-cytochrome *c* reductase and aniline

	hydroxylase were increased with 59% and 170%, respectively, as well as the amount of cytochrome P-450 with 45%.
Conclusion	A single injection or 3 successive injections of nicotinamide (500 mg/kg bw) increased NADPH-cytochrome *c* reductase and aniline hydroxylase activities of rat liver microsomes without changing cytochrome P-450 content. Oral administration of nicotinamide for 2 weeks resulted in statistically significant increase in cytochrome P-450, indicating nicotinamide as an inducer of cytochrome P-450 though its potency was weak.
Rev. note	Microsomes of rats from experiment 2 or 4 were treated with several concentrations of aniline. At 1 mM a low affinity form of aniline hydroxylase was shown to be present in microsomes isolated from nicotinamide-treated rats next to the high affinity form present in control-rats.
Reliability	4.

Title	Pharmacokinetics and biochemistry studies on nicotinamide in the mouse.
Date of report	1994.
Reference	91.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
GLP	No data
Guideline	Not applicable.
Stat. method	Not applicable.
Procedure	In male mice (10-15 weeks) tumours were implanted. The animals received a single dose of nicotinamide (100, 200, 300 and 500 mg/kg i.p.) Plasma concentrations of nicotinamide and nicotinamide N-oxide were determined at several time points upto 30 hours post dosing. Tumour concentrations of nicotinamide and NAD and energy charge (ATP, ADP, AMP were determined). Plasma serotonin concentration was measured over a 20 min period to investigate whether nicotinamide induced the conversion of tryptophan to serotonin by inhibition of tryptophan hydrolase (the first enzyme involved in the pathway that converts tryptophan to NAD)
Results	In plasma only nicotinamide and nicotinamide N-oxide were found, no other metabolites. Nicotinamide showed a biphasic elimination pattern, which may have been caused by backconversion of the metabolite nicotinamide N-oxide to the parent compound or by an increase of plasma nicotinamide released from "storage" NAD. Tumour concentrations of nicotinamide reached plasma concentrations rapidly. The NAD concentration in tumours showed a statistically significant increase with increased nicotinamide dose (considerable scatter of data). No relationship between tumours energy charge and nicotinamide concentration became apparent. Plasma levels of serotonin did not increase after nicotinamide administration.
Conclusion	N-oxidation is the most important metabolic pathway in mice Nicotinamide shows biphasic clearance in mice.
Rev. note	The mouse appears to be a less suitable model for human nicotinamide exposure. The study was conducted in order to clarify the effect of radiation on murine tumors after sensitization with nicotinamide. N-oxide has been shown to be a weak radiosensitizer in mice.
Reliability	2.

Title	Nicotinamide pharmacokinetics in normal volunteers and patients undergoing palliative radiotherapy.
Date of report	1996.
GLP	No data.
Reference	92.
Test substance	CAS 98-92-0 (Nicotinamide; comm. available vitamin tablet), purity not indicated.
Guideline	Not applicable.
Stat. method	Weighted non-linear least squares regression analysis; AUC's determined by trapezium rule.

Test system 6 normal volunteers were given single doses of nicotinamide up to 9 g, both after overnight fasting and following a light meal. Two formulations were evaluated: tablet (0.5 g) and a solution made up in orange juice (~ 150 ml). Blood samples were taken every 15 min for the first 2 h, at 3, 4 and 8 h, and for 4 volunteers also at 24 h.
6 patients undergoing radiotherapy were given multiple administrations: 2 times weekly for 3 weeks or on weekdays for 1 week (+ 1 add. dose). Blood samples were taken 1, 2 and 3 h after administration.

Analysis Concentrations of nicotinamide were determined in methanol extracts of plasma by HPLC using a reversed-phase ion-pairing technique.

Results

	Volunteers						**Patients**	
Dose	**6-9 g**		**3g**				**5-6g**	
	Fasted	**Fed**	**Fed**	**Fasted**	**Fed**	**Fasted**	**2/week**	**workdays**
Formulation	**Tablet**	**Liquid**	**Liquid**	**Liquid**	**Tablet**	**Tablet**	**Tablet**	**Tablet/liquid**
T_{max}	0.7-1.7	0.5-1.5	0.5-2.0	0.5-1.3	1.8-3.0	0.9-2.0	1-3	4 / 0.5-4
C_{max}	1.0-1.7	0.9-1.3	0.3-0.6	0.5-0.6	0.3-0.5	0.3-0.7	0.8-1.7	0.8 / 1.1
AUC(8h)	6.3-7.9	4.0-7.1	1.6-3.1	2.3-3.3	1.4-2.9	1.3-3.2	7.9-28*	9.0 / 13*
Toxicity		nausea						Flushing, anorexia, nausea, headache

* over 24 h period

Conclusion In general, more rapid absorption gave rise to higher peak concentrations. Peak concentrations were generally slightly higher following liquid preparation, but the toxicity in the form of nausea was increased. No correlation was found between the incidence of toxicity and peak concentration, time to reach the peak or the main metabolites. Side effects were observed for 6 g doses.

Rev. note Journal article.

Reliability 2.

Title Nicotinic acid or nicotinamide?

Date of report 1996.

GLP Not applicable.

Reference 103.

Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.

Guideline Not applicable.

Stat. method Not applicable.

Findings For incorporation into NAD rat liver and -kidney prefer nicotinic acid as substrate, while rat pancreatic β-cells, erythrocytes and testes prefer nicotinamide. The mitochondrial fraction of liver cells exclusively utilises nicotinamide as substrate.
Microbial activities in the digestive tract will determine to a great extent the form of niacin that is absorbed from the intestine. Deamidation by micro-organisms was reported in the rat, rabbit, guinea-pig, pig, horse and non-human primates, but not in man, dog and cat.
Nicotinamide after oral administration is mainly excreted as N'-methylnicotinamide in the urine of dog (100%), rat (30-50%) and man (30-50%); In man 35-45% is found as 6-pyridone (N'-methyl-6-pyridone-5-carboxyamide), in pig 10% and in rat 3-5%.
One publication reports absorption of nicotinamide by passive diffusion (proportionally to dose), while nicotinic acid is absorbed by a sodium-independent carrier. In other publications show a combination of both ways for both vitamers .

Conclusion There are functional, organ and species-related differences between nicotinamide and nicotinic acid with regard to digestion, absorption, organ metabolism and NAD biosynthesis (cellular and sub-cellular).

Rev. note Review article covering biosynthesis of NAD and non-vitamin related effects.

Reliability 4

Title Nicotinamide deamidase from rabbit liver.

Date of report 1966.
Reference 105.
Test substance CAS 98-92-0 (Nicotinamide-7-14C and nicotinamide with a specific activity of 16 µC/mmol), purity not indicated.
GLP No.
Results Nicotinamide is converted to nicotinic acid by nicotinamide deamidase, mostly in the liver. About 60% of the amidase activity in the liver is located in the microsomal fraction.
The enzyme is susceptible to inhibition by several substances and normal tissue contains inhibitory material. The amidase activity is influenced by pH (optimum ≈ 8)
Rev. note Journal article.
Reliability 4.

Title Nicotinamide deamidase from mammalian liver.
Date of report 1965.
Reference 109.
Test substance CAS 98-92-0, ^{14}C-Nicotinamide, specific activity 6.0-9.9, purity not indicated.
GLP No.
Remark Nicotinamide is metabolised to nicotinic acid by a microsomal deamidase in rat and rabbit. This is considered to be the first step in the biosynthesis of nicotinamide adenine dinucleotide (NAD). The activity of the enzyme is increased in presence of BSA (bovine serum albumin), which suggests the existence of an endogenous competitive inhibitor for the enzyme. In liver homogenate Km values (mM) of 1100 and 128 were found for rats and rabbits, respectively. In presence of BSA these values were 177 and 89. In pigeons the same enzyme is found, however, located in the sub-cellular fraction and with a rather different affinity for the substrate.
Rev. note Journal article
Reliability 4.

Title The Pharmacokinetics of nicotinamide in humans and rodents
Date of report 1995.
GLP No data.
Reference 111.
Test substance CAS 98-92-0 (Nicotinamide; comm. available vitamin tablet), purity not indicated.
Guideline Not applicable.
Stat. method Student's t-test.
Test system Eight normal adult male volunteers were given single doses of nicotinamide after overnight fasting. Two formulations were evaluated: powdered pure nicotinamide and a tablet Enduramide (0.5 g) both in low and high dose (see table). Different doses and formulations were studied in each volunteer (separated by at least 1 week). Blood samples were taken every 15 min for the first 2 h, and at regular intervals thereafter upto 12 hours.
Analysis Plasma concentrations of nicotinamide were determined by reverse-phase HPLC.
Results

Dose [mg/kg bw]	**2.5**	**6.7**	**25**	**26.6**
Formulation	**powder**	**tablet**	**powder**	**tablet**
T_{max} (h)	0.3	1.0	0.5	1.9
C_{max} (µg/mL)	3.3	2.1	42	16
AUC	3.0	4.5	187	107
T1/2	0.6	1.0	3.5	2.7

Conclusion The powder was absorbed more rapidly absorption and gave rise to higher peak concentrations. Kinetics were non-linear, since a 10-fold increase in dose gave a 13-fold increase in C_{max} and a 62-fold increase in AUC (similar pattern for the tablet). This means that bioavailability is higher or clearance is lower at the high dose.
Rev. note The primary metabolite in both man and rodents is N'-methylnicotinamide. The non-linear kinetics may be related to depletion of S-adenosylmethionine (the methyl donor).
Journal article

Reliability 2

Title Nicotinic acid and Nicotinamide
Date of report 1984.
Reference 112.
Test substance CAS 98-92-0, ^{14}C-Nicotinamide, purity not indicated.
GLP No.
Results Nicotinamide readly passes between cerebrospinal fluid and plasma. Its entry is sited at the choroid plexus and regulated by a high affinity accumulation system.

Mouse
In vivo studies in mice showed that little or no hydrolysis of nicotinamide occurred in the digestive tract. The major excretion product in mice is N^1-methylnicotinamide-*N^1*-oxide.

Rat
In rats 500 mg/kg nicotinamide (dose regimen not indicated) was excreted as nicotinamide (65% of dose), N^1-methylnicotinamide (8%), nicotinuric acid (6%) and nicotinamide *N*-oxide (7%); at 5 mg/kg 34% as N^1-methylnicotinamide, 5% as nicotinamide and 5% as N^1-methyl-2-pyridone-5-carboxamide.

Human
In healthy humans at 1 g (n=3) N^1-methyl-2-pyridone-5-carboxamide and N^1-methylnicotinamide were the main urinary metabolites. At 3 g (n=1) nicotinamide and N^1-methyl-4-pyridone-3-carboxamide appeared the main metabolites excreted. Excretion pattern in schizophrenic patients differed from that in normal volunteers used as controls.
Conclusion Nicotinamide metabolism is different in various species. The 2-pyridone metabolite is important in human but not in rat.
Rev. note Review paper covering (analytic) content in food, metabolites, defiencies, requirements.
Reliability 4.

Title Niacinamide and Niacin, CIR report, scientific literature review, 2001.
Date of report 2001.
Reference 113.
Test substance CAS 98-92-0, Nicotinamide, purity not indicated.
GLP No.
Method Urinary excretion of nicotinamide and metabolites in mice (CD-1(ICR), guinea pigs (Hartley) and hamsters was determined before (samples over 42 days) and after 500 mg/kg nicotinamide i.p. (samples over 4 days)
Results

Species/metabolite [%]	**Mouse**		**Guinea pig**		**Hamster**	
	before	**after**	**before**	**after**	**before**	**after**
Nicotinamide	18		3		44	
Nicotinamide *N*-oxide	35	79.7	3		15	
N1-methylnicotinamide	16	4.9	11		10	
N1-methyl-2-pyridone-5-carboxamide	20	11.2	80		21	
N1-methyl-4-pyridone-3-carboxamide	11	6.3	3		10	
Nicotinic acid				7.7		50.4
Nicotinuric acid				79.5		26.3

Conclusion Nicotinamide metabolism is different in various species.
Rev. note Review paper on biology and toxicology
Reliability 4.

5.2. Acute toxicity

5.2.1. Acute oral toxicity

Title	Determination of the acute oral toxicity in rats of nicotinic acid-amide.	
Date of report	1979.	
GLP	No.	
Reference	9.	
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.	
Guideline	Not indicated.	
Stat. method	LD50 was determined using the method of Weil.	
Test system	**Species**	Rat (Wistar), mean body weight: 117.1±1.4 g for males; 110.2±1.5 g for females.
	Source	TNO.
	No. of animals	10/sex/treatment.
	Dosage	Single oral administration (gavage) of 2.0, 2.4, 2.9, 3.4 and 4.2 g/kg bw (40% (w/v) aqueous solution); no controls; feed was withheld overnight prior to dosing.
	Observations	Mortality/clinical signs during 14 days. Necropsy on survivors.

Results

Effect/Dose [g/kg bw]		**2.0**		**2.4**		**2.9**		**3.4**		**4.2**	
Sex	**Day**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Mortality	1-14	0/10	0/10	0/10	0/10	1/10	2/10	5/10	4/10	8/10	8/10
Clinical signs[(A)]	1-14	Not detailed									
Necropsy[(B)]	14	Not detailed									

Clinical symptoms: After a few hours, sedation, tremors and convulsions were observed. Coma frequently preceded death. Most animals died on day 1.
Necropsy: Only mottled kidneys were observed in an occasional rat.

Conclusions	Oral LD_{50} = 3.53 g/kg bw (95%, 3.21-3.88) for male and 3.54 g/kg bw (95%, 3.16-3.96) for female.
Rev. note	The study was not performed under GLP. It is not clear if symptoms are observed daily. Body weights were not measured. No individual data were presented.
Reliability	2.

Title	Acute oral LD50 toxicity study niacinamide.	
Date of report	1977.	
GLP	No.	
Reference	10.	
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.	
Guideline	Not mentioned.	
Stat. method	Not applicable.	
Test system	**Species**	Rat (Wistar), males/females, weight 200-300 g.
	Source	Not indicated.
	No. of animals	5/sex/treatment.
	Dosage	Single oral administration (gavage) of 2.0, 3.2, 4.0, 5.0, 6.3, 8.0, 10.0 and 16.0 g/kg bw (vehicle: water); no controls; feed was withheld 24 h prior to dosing.
	Observations	Mortality/clinical signs: daily for 14 days.

Results

Effect\Dose [g/kg bw]		**2.0**		**3.2**		**4.0**		**5.0**		**6.3**		**8.0**		**10.0**		**16.0**		**DR**	
Sex	**Day**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Mortality[(A)]	1-14	0/5	0/5	0/5	0/5	0/5	0/5	0/5	3/5	2/5	3/5	3/5	4/5	5/5	5/5	5/5	5/5	x	x
Clinical signs[(B)]	1-14	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	x	x

(A) Most animals died on day 1.
(B) Consisted of: ruffled and unkempt coats, lethargy, coma.

Conclusions Oral LD_{50} = 7.1 g/kg bw (95%, 6.0-8.2) for males and 5.5 g/kg bw (95%, 4.5-6.7) for females.
Rev. note The study was not performed under GLP.
Body weight gain was not studied.
Reliability 2

Title Acute oral toxicity evaluations.
Date of report 1973.
GLP No.
Reference 11.
Test substance Nicotinamide, purity not indicated.
Guideline Not mentioned
Stat. method LD50 calculated using the method of Litchfield and Wilcoxan.
Test system Species Mouse (Tylers original), males/females, mean body weight 20±2 g.
No. of animals 5/sex/treatment.
Dosage Single oral administration (gavage) of 2000, 2500, 3000, 3500 and 4000 mg/kg bw (100 mg/ml solution); vehicle not indicated; no controls; feed was withheld overnight prior to dosing.
Observations Mortality/clinical signs: daily for 14 days.

Results

Effect\Dose [mg/kg bw]	Day	2000	2500	3000	3500	4000
Mortality[(A)]	1-14	0/10	1/10	3/10	7/10	10/10

Clinical signs: General loss of activity was seen in high dose animals within 60 min. of dosing. Survivors were asymptomatic after 24 h.

Conclusions Oral LD_{50} = 3100 mg/kg bw (95%, 2844-3379).
Rev. note Body weight measurements and necropsy were not performed. Clinical signs were reported as a summary only. Only total mortality of male and female is given.
This study was not performed under GLP.
Reliability 2.

Title Acute oral toxicity evaluations.
Date of report 1973.
GLP No.
Reference 11.
Test substance Nicotinamide, purity not indicated.
Guideline Not mentioned (range finding study)
Test system **Species** Mouse (Tylers original)
No. of animals 2 (sex not indicated).
Dosage Single oral administration (gavage) of 500, 1000, 2500 and 5000 mg/kg bw (100 mg/ml solution); vehicle not indicated; no controls
Observations Mortality: daily for 7 days.
Results **Mortality** 0/2, 0/2, 0/2 and 2/2 at 500, 1000, 2500 and 5000 mg/kg bw
Symptoms Loss of activity in high dose animals within 60 min of dosing.
Rev. note Information limited to the above mentioned
Reliability 4.

Title Acute oral toxicity evaluations.
Date of report 1973.
GLP No.
Reference 11.
Test substance Nicotinamide, purity not indicated.
Guideline Not mentioned (range finding study)
Test system **Species** Rat (Wistar)
No. of animals 2 (sex not indicated).
Dosage Single oral administration (gavage) of 500, 1000, 2500 and 5000

		mg/kg bw (200 mg/ml solution); vehicle not indicated; no controls
	Observations	Mortality/symptoms: daily for 7 days.
Results	**Mortality**	0/2, 0/2, 0/2 and 2/2 at 500, 1000, 2500 and 5000 mg/kg bw
	Symptoms	Loss of activity in high dose animals within 120 min of dosing.
Rev. note	Information limited to the above mentioned.	
Reliability	4.	

Title	Acute oral toxicity evaluations.	
Date of report	1973.	
GLP	No.	
Reference	11.	
Test substance	Nicotinamide, purity not indicated.	
Guideline	Not mentioned (range finding study)	
Test system	**Species**	Rabbit (New Zealand White)
	No. of animals	2 (sex not indicated).
	Dosage	Single oral administration (gavage) of 500, 1000, 2500 and 5000 mg/kg bw (200 mg/ml solution); vehicle not indicated; no controls
	Observations	Mortality: daily for 7 days.
Results	**Mortality**	0/2, 0/2, 1/2 and 2/2 at 500, 1000, 2500 and 5000 mg/kg bw
	Symptoms	Loss of activity in high dose animals within 60 min of dosing.
Rev. note	Information limited to the above mentioned.	
Reliability	4.	

Title	Studies on the toxicity and pharmacology of nicotinic acid.	
Date of report	1939.	
GLP	No.	
Reference	96.	
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.	
Guideline	Not applicable.	
Stat. method	Not applicable.	
Test system	**Species**	Mouse; 5-10 animals/treatment
	Dosage	Single dose, oral and subcutaneous (10% w/v aqueous solution).
Results	Mortality was observed after subcutaneous administration of ≥ 1.8 g/kg bw of nicotinamide within 12-36 hours of administration. Preceding death, animals became unable to move and were atactic, respiration became slow and cyanosis was observed for both substances administered.	
Conclusion	LD50 oral ≈ 2.2 g/kg bw; LD50 subcutaneous ≈ 2.9 g/kg bw.	
Rev. note	LD50 determined by reviewer from mortality%-dose curve. Non GLP and primarily only results given.	
Reliability	2.	

Title	Studies on the toxicity and pharmacology of nicotinic acid.	
Date of report	1939.	
GLP	No.	
Reference	96.	
Test substance	Nicotinic acid, sodium nicotinate and nicotinamide, purity not indicated.	
Guideline	Not applicable.	
Stat. method	Not applicable.	
Test system	**Species**	Rat.
	Dosage	Single dose, oral and subcutaneous (10% w/v aqueous solution).
Results	Similar to mouse; symptoms likewise non-characteristic.	
Conclusion	LD50 oral ≈ 2.7 g/kg bw; LD50 subcutaneous ≈ 3.4 g/kg bw.	
Rev. note	LD50 determined by reviewer from mortality%-dose curve. Non GLP and primarily only results given.	
Reliability	2.	

5.2.2. Acute Dermal Toxicity

Title	Testing the acute toxicity after a single dermal application in rabbits.	
Date of report	1990.	
GLP	Yes.	
Reference	12.	
Test substance	CAS 98-92-0 (Nicotinamide), purity 99.8%.	
Guideline	OECD 402, 84/449/EEC.	
Stat. method	Not applicable.	
Test system	**Species**	Rabbit (White Russian), weight males 2.38-2.95 kg, females 2.48-2.93 kg.
	Source	Asta Pharma AG.
	No. of animals	5/sex/treatment.
	Dosage	Single dermal application (occlusive for 24 h) of 2000 mg/kg bw in water; no controls; feed was withheld 16 h prior to dosing.
	Observations	Mortality/clinical signs: 0-6 hrs, and daily thereafter for 14 days. Body weight on day 0, 7 and 14. Necropsy on day 14.

Results

Effect\Dose [mg/kg bw]	**Day**	**2000**	
Sex		**M**	**F**
Mortality	0-14	None	None
Clinical signs[(A)]	0-14	+	+
Body weight	0-14	No treatment-related effects.	No treatment-related effects.
Necropsy	14	No treatment-related effects.	No treatment-related effects.

(A) A slight reddening was observed immediately after removal of the patches in all animals. In some animals the reddening was present till the end of the observation period.

Conclusions	Dermal LD_{50} >2000 mg/kg bw.
Reliability	1.

5.2.3. Acute Inhalation Toxicity

No data

5.2.4. Acute Toxicity, other Routes

Title	Drug-biomolecule interactions: drug toxicity and vitamin coenzyme depletion	
Date of report	1975	
GLP	No	
Reference	35	
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.	
Guideline	Not applicable	
Stat. method	Litchfield and Wilcoxon	
Test system	**Species**	Young adult Swiss albino and Charles River mice
	No. of animals	5 to 6 groups of 10-30 mice per treatment
	Weight	20-32 g
	Dosage	Not indicated
	Volume administered	0.2 ml in aqueous solution
	Route of administration	Intraperitoneal
	Post exposure observation period	7 days
Results	LD_{25} = 1940 mg/kg bw; Clinical signs: sedation	

Rev. note	Journal article	
Reliability	2.	

Title	The pharmacological effects of massive doses of nicotinamide.	
Date of report	1953.	
GLP	No.	
Reference	39.	
Test substance	CAS 98-02-0 (Nicotinamide), purity not indicated.	
Guideline	Not indicated.	
Stat. method	LD50 was determined graphically from the dose response curve.	
Test system	**Species**	Mouse, no further indications.
	No. of animals	20/dose.
	Dosage	Intravenous or intraperitoneally, no data on dosage levels.
Results	Death usually occurred within 6-12 hours. Animals first show pronounced tachypnoea and later prostration and shallow respiration.	
Conclusions	Intravenous LD_{50} 1620 mg/kg bw . Intraperitoneal LD_{50} 1800 mg/kg bw.	
Rev. note	The information in the report is essentially confined to what is included in the current summary. Journal article.	
Reliability	4.	

Title	Potentiation of insulin hypoglycaemia by nicotinyl taurine (β-nicotinamidoethanesulphonic acid.	
Date of report	1946	
GLP	No.	
Reference	53.	
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.	
Guideline	Not indicated.	
Stat. method	Not indicated.	
Test system	**Species**	Mouse
	No. of animals	8/treatment
	Dosage	Not indicated.
	Observations	Not indicated
Results	LD_{50} 2600 mg/kg bw. LD_{100} 4000 mg/kg bw.	
Rev. note	The information in the report was essentially confined to what is included in the current summary. Journal article.	
Reliability	4.	

Title	Effect of N-(3,5-dichlorophenyl)succinimide on the histological pattern and incidence of kidney tumors induced by streptozotocin in rats.	
Date of report	1977.	
GLP	No.	
Reference	88.	
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.	
Guideline	Not indicated.	
Test system	**Species**	Male Sprague Dawley rats (160-190 g).
	Source	CLEA Japan, Inc., Tokyo.
	No. of animals	Control: 15, treated: 11.
	Dosage	Treatment on day 1 with two doses of nicotinamide (350 mg/kg i.p.in physiologic saline).
	Post exposure period	40 weeks
Investigations	**General**	Body weight.
	Clinical	Hematology (timing not stated): erythrocyte and leukocyte count,

pathology hematocrit and hemoglobin.
Clinical chemistry (timing not stated): ALAT, ASAT, alkaline phosphatase (ALP), total protein and blood urea nitrogen.
Necropsy Macroscopy: tumour incidence and localization.
Organ weights: liver, spleen and both kidneys.
Microscopy: liver, spleen, both kidneys and any other organ appearing abnormal.

Results

	Group	
Parameter	**Control**	**Treated**
Body weight	No treatment related effects	
Hematology	No treatment related effects	
Clinical chemistry		
ALAT		I
ALP		I
Blood urea		d
Organ weights	No treatment related effects	
Microscopy	-	-
Tumor incidence	No tumours were found in either group.	

Conclusions A single treatment of two times 350 mg/kg nicotinamide i.p. did not cause any toxic effects in male rats within 40 weeks.
Rev. note Journal article.
Reliability 4.

Title Studies on the toxicity and pharmacology of nicotinic acid.
Date of report 1939.
GLP No.
Reference 96.
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline Not applicable.
Stat. method Not applicable.
Test system **Species** Rabbit and cat.
Dosage Single intravenous injection (10% w/v aqueous solution).
Results The blood pressure of rabbits and cats under urethane and chloralose anesthesia was not influenced by nicotinamide for doses up to 1 g/kg bw.
Rev. note Non GLP and only results given.
Reliability 4.

Title Toxicity of nicotinic acid and some of its derivatives.
Date of report 1946.
GLP No.
Reference 41.
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline Not mentioned
Stat. method Not mentioned.
Test system **Species** Rat, males/females, body weight 50-100 g.
No. of animals Not reported.
Dosage Subcutaneous administration (injection) of unknown doses.
Observations Mortality.
Results No individual results reported.
Conclusions Subcutaneous LD_{50} = 1680 mg/kg bw for nicotinamide.
Rev. note Journal article.
Reliability 4.

5.3. Corrosiveness/Irritation

A Skin irritation/Corrosion

Title Prüfung der Ätz-/Reizwirkung nach einmaliger Applikation an der Haut des Kaninchens (Patch –Test).
Date of report 1985.
GLP No.
Reference 17.
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline OECD 404, 84/449/EEC.
Stat. method Not applicable.
Test system Species Rabbit (White Russian), weight 2.5-2.7 kg.
Source Asta-Werke AG.
No. of animals 1 male and 2 female/treatment.
Dosage Single dermal application of 0.5 g on ca. 6.25 cm^2 of clipped dorsal skin under occlusion for 4 hours.
Observations Skin observations at 1 h and daily thereafter for 9 days.

Results

Animal	1		2		3	
Time	**E**	**O**	**E**	**O**	**E**	**O**
1 h	1	0	0	0	0	0
24-72 h	0	0	0	0	0	0

E=erythema O=oedema

Conclusion Not irritating.
Rev. note The test was performed under occlusion, which represents a worst case scenario. The validity of the results is not affected.
Results were reported for 72 h only.
The study was not performed under GLP.
Reliability 2.

B Eye Irritation/Corrosion

Title Acute eye irritation test in the rabbit.
Date of report 1990.
GLP Yes.
Reference 18.
Test substance CAS 98-92-0 (Nicotinamide), purity 99.9%.
Guideline OECD 405, 84/449/EEC directive annex V of 67/584/EEC.
Stat. method Not applicable.
Test system **Species** Rabbit (New Zealand White), weight 2.54-2.97 kg.
No. of animals 3 females.
Dosage Single application of ca. 100 mg in the right eye.
Observations At 1, 24, 48 and 72 h (numerical evaluation according to Draize). On day 7 the reversibility was assessed.

Results

Animal	**1**				**2**				**3**			
Effect	**C**	**I**	**Conj[A]**		**C**	**I**	**Conj[A]**		**C**	**I**	**Conj[A]**	
Time			**Red**	**Ch**			**Red**	**Ch**			**Red**	**Ch**
1 h	d[B]	1	2	2	0	1	2	2	d[B]	1	2	3
24 h	1	1	2	1	1	1	2	2	1	1	2	3
48 h	1	1	1	0	1	1	2	2	1	1	3	2
72 h	1	0	0	0	1	0	1	1	1	1	3	2
7 d	0	0	0	0	0	0	0	0	-[C]	-	-	-

C=corneal opacity I=Iris Conj=conjunctiva Red=redness Ch=chemosis.
(A) Severe discharge was observed.
(B) d = dulling of the normal lustre of the corneal surface
(C) - = animal killed for humane reasons

Conclusion irritating
Rev. Note At 72 h effects are still seen in animal 3

Reliability 1.

Title Toxikologische Prüfung auf Reizwirkung am Kaninchenauge nach einmaliger Applikation.
Date of report 1985.
GLP No.
Reference 19.
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline OECD 405, 84/449/EEC.
Stat. method Not applicable.
Test system
Species Rabbit (White Russian), weight 2.1-2.35 kg.
No. of animals 3 males.
Dosage Single application of 0.1 g in the right eye; left eye untreated control.
Observations Eye irritation (numerical evaluation according to Draize) and clinical symptoms at 1, 24, 48 and 72 h and then daily until 21 days.

Results

Animal	**1**				**2**				**3**			
Effect	C	I	**Conj(A)**		**C**	**I**	**Conj(A)**		**C**	**I**	**Conj(A)**	
Time			**Red**	**Ch**			**Rec**	**Ch**			**Red**	**Ch**
1 h	1	0	1	2	1	0	1	2	1	0	1	2
24 h	1	1	2	2	2	1	2	3	2	1	2	2
48 h	1	1	2	1	1	1	2	2	2	1	2	2
72 h	1	1	2	1	1	0	2	2	2	1	2	2

C=corneal opacity I=Iris Conj=conjunctiva Red=redness
Ch=chemosis
(A) Discharge was also observed.
All symptoms were reversible within one week, except for hyperaemia of the conjunctiva in one animal, which lasted until the twelfth day. No systemic effects were observed.

Conclusion Irritating.
Reliability 1.

Title Studies on eye irritation caused by chemicals in rabbits - 1. A quantitative structure-activity relationships approach to primary eye irritation of chemicals in rabbits.
Date of report 1990.
Reference 93.
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
GLP No data.
Remark Nicotinamide is classified as a moderate to severe irritant, based on days needed for recovery. This means nicotinamide induces corneal involvement or irritation that persists for more than 24 hours, but recovers within 21 days after treatment.
Rev. note Review article.
Reliability 4.

5.4. Skin Sensitisation

Title Prüfung auf sensibilisierende Eigenschaften an der Haut des Meerscheinchens (Maximisierungs-Test)
Date of report 1986.
GLP No.
Reference 114.
Test substance CAS 98-92-0, Nicotinamide, purity not indicated.
Guideline OECD 406, 84/449/EEC.
Stat. method Fisher test.
Test system
Species Guinea-pig (Pirbright White (Bor: DHPW)), weight 380-470 9
No. of animals 10/sex/treatment group.
Procedure As per OECD 406 (maximisation test): Intradermal induction (1% in

saline (0.9% NaCl)) on day 1, topical induction on day 8 (50% in saline), challenge on day 22 (50% in saline), skin reading after 24 and 48 h (day 24 and 25).

Observations Skin reactions 24 and 48 hours after the challenge exposure. Body weight on day 2 and weekly thereafter.

Results

Dose/effect	Control	Test substance
Body weight	No treatment related effects	
Challenge		
No. with positive erythema score (24/48h)	0/0	4/3

Conclusions Negative

Rev. note The outcome of the test does not allow the conclusion that the substance is a sensitiser. In order to elucidate the outcome a rechallenge would have been appropriate. As this rechallenge is not performed, the reliability of the results is lowered.

Minor remark No information on clinical signs was included in the report. The scoring system used is not according to Magnusson and Klogman, but according to Draize.

Reliability 2 No rechallenge performed.

Title Nicotinamide, pharm, Testing the cutaneous sentizing properties in the Guinea Pig (Buehler Test)

Date of report 1988.

GLP No.

Reference 115.

Test substance CAS 98-92-0, Nicotinamide, purity not indicated.

Guideline OECD 406, 84/449/EEC.

Stat. method Fisher test.

Test system

Species Guinea-pig (Pirbright White (Bor: DHPW)), weight 413-470 9

No. of animals 5/sex/treatment group, 3 males and 2 females in controls.

Procedure As per OECD 406 (Buehler test): Induction (50% in saline (0.9% NaCl)) on day 1, 8 and 15, challenge on day 30 (50% in saline), skin reading after 24 and 48 h (day 31 and 32).

Observations Skin reactions 24 and 48 hours after the challenge exposure. Clinical signs
Body weight on day 2 and weekly thereafter.

Results

Dose/effect	Control	Test substance
Body weight	No treatment related effects	
Clinical signs	No treatment related effects	
Challenge		
No. with positive erythema score (24/48h)	0/0	0/0

Conclusions Not sensitising.

Rev. note The number of animals in this test is too low to allow a proper evaluation. According to OECD 406 at least 20 treated and 10 control animals are needed.

Reliability 2 Limited number of animals.

5.5. Repeated Dose Toxicity

Title Nicotinamide: 4-week oral toxicity study after repeated administration in rats and a subsequent 6-week recovery period.

Date of report 1993.

GLP Yes.

Reference 13.

Test substance CAS 98-92-0 (Nicotinamide), purity 99.8%.

Guideline OECD 407, 1981.

Stat. method Dunnet test, Steel test.

Test system

Species Rat (WISW), age: 6 weeks (males), 7 weeks (females); body weight: 146-186 125-165 g (females).

	Source	Winkelmann Versuchstierzucht GmbH & Co, Borchen, Germany.
	No. of animals	10/sex/control and high dose, 5/sex/low dose. (5/sex in control and high dose for recovery period).
	Dosage	Daily oral administration by gavage of 215 or 1000 mg/kg bw (vehicle deionized water; dosing volume 4.64 ml/kg); controls: tap water.
	Exposure period	28 days.
	Post exposure period	6 weeks.
Investigations	**General**	Behavior and general condition (daily); mortality (twice daily); food consumption (weekly); body weight (weekly); reflexes (pain, pinna and corneal, weekly); eyes, hearing and teeth in week 1 and 4.
	Clinical pathology	Hematology (week 4 and 10): erythrocytes, hematocrit, hemoglobin, (differential) leukocyte count, mean corpuscular haemoglobin (concentration), mean corpuscular volume, platelet count Clinical chemistry (week 4 and 10): alanine aminotransferase (ALAT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase (ASAT), blood urea, calcium, chloride, cholinesterase, creatine kinase, creatinine, γ-glutamyltransferase, glucose, glutamate dehydrogenase, inorganic phophate, potassium, serum electrophoresis, sodium, total bilirubin, total cholesterol, total protein and triglycerides Urinalysis (week 4 and 10): bilirubin, glucose, hemoglobin/erythrocytes, ketones, leucocytes, nitrite, osmolality, pH-value, protein, urobilinogen.
	Necropsy	Macroscopy: external body surface, all gross lesions, adrenal glands, bone marrow (smear), brain, cecum, colon, duodenum, heart, ileum, jejunum, kidneys, liver, lungs, ovaries, rectum, spleen, stomach and testes. Organ weights: adrenals, brain, heart, kidneys, liver, ovaries, spleen and testes Microscopy: all organs investigated macroscopically.
Analysis	Stability of the test substance in the concentrations to be used (46 and 215 mg/ml) was assessed before start of the study. Concentration of the test substance in each concentration for administration was verified by HPLC analysis in samples taken in week 1 and 3.	

Results

Dose	**0 mg/kg**		**215 mg/kg**		**1000 mg/kg**		**Dose related**	
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Mortality [A]	No test substance related deaths occurred							
Clinical Signs [B]	No test substance related effects.							
Body weight gain [C]			dc		dc		x	
Food consumption [D]			dc		dc			
Reflexes/eyes/hearing /teeth	No test substance related effects.							
Hematology	No test substance related changes of toxicological significance.							
Clinical chemistry [E]								
ASAT				i	ic	i		
ALAT				ic	ic	ic		x
Cholesterol				i		ic		
ALP					ic			
Blood urea				i	ic	ic		
Albumin					ic			
Total bilirubin						ic		

Calcium				ic		ic		
Urinalysis	No statistically significant changes were observed.							
Necropsy								
Macroscopy	No test substance related changes were seen.							

Liver weight (4 weeks)			i^{r}	$i^{r, a}$	ic^{r}	$ic^{r, a}$	x	x
Kidney weight (4 weeks)					ic^{r}			
Adrenal weight (4 weeks)					ic^{r}			
Brain weight (4 weeks)			ic^{r}					
Spleen weight (4 weeks)					dc^{a}			
Heart weight (10 weeks)						$dc^{r, a}$		
Kidney weight (10 weeks)					dc^{a}			
Microscopy (F)			+		+	+		

Where i=increase; d=decrease; ic=statistically significant increase; dc=statistically significant decrease; ^{a}=absolute; ^{r}=relative.
(A) One control animal was sacrificed after blood sampling.
(B) Incidental eschar formation and alopecia.
(C) Differences in body weight gain (8-10%) disappeared during the recovery period.
(D) Differences in food consumption (maximum 11%) disappeared after week 2 of treatment.
(E) All changes were only minimal to slight and within normal ranges for rats of this strain and age.
(F) Only changes in the liver and spleen were considered test substance related; liver: mild hepatocellular induction/hypertrophy; spleen: relatively reduced extramedullary hematopoiesis (high dose only). After the recovery period only the spleen was affected in females only.

Analyses of test substance The test substance was stable.
Concentrations as measured (100-103%) were within acceptable ranges (90-110%) of the nominal concentrations.

Conclusions NOAEL = 215 mg/kg bw

Rev. note Reduced body weight gain and food consumption were seen in males only. The increased relative liver weight (males 6-13%) and microscopic liver changes in males were considered an adaptive reaction to the test substance. The effects in females were more pronounced (relative liver weight –9-27%). In addition in females the effects on the spleen were not completely reversible.
Only 2 dose levels were investigated.

Reliability 1.

Title The effect of excessive nicotinamide feeding on rabbits and guinea pigs.

Date of report 1944.

Reference 57.

Test substance CAS 98-92-9 (Nicotinamide), purity not indicated.

GLP No.

Method test 1 Rabbits (weanlings, 1250 g mean weight) were fed two different diets, A and B, both with 1% or 2% nicotinamide. After 20 days of exposure, animals were sacrificed and liver samples were analysed for fat content. Urine was collected in 3 animals per dose over a 48-hour period (day 15 and 16), for urinary N-methylnicotinamide analysis.

Results test 1 No statistically significant effects on growth, liver fat content or urinary N-methylnicotinamide excretion were seen. A slight decrease in body weight gain was seen with increasing nicotinamide content in diet A.

Method test 2	Guinea pigs (7 days old, mean weight 124 g) were fed diet 1 with 1% nicotinamide, or diet 2 with 0.5, 1 or 2% nicotinamide for 4 weeks. After exposure, animals were sacrificed and liver samples were analysed for fat content. Urine was collected from 3 animals per dose over a 48-hour period (day 16 and 17), for urinary N-methylnicotinamide analysis. All animals ate sparingly for the first 5 days, so only the data of the three weeks following those 5 days were analysed. No effects on body weight gain, liver fatty acid content or urine N-methylnicotinamide content.
Results test 2	No statistically significant effects on growth, liver fat content or urinary N-methylnicotinamide excretion were seen.
Rev. note	Journal article Only limited parameters are investigated. Animals used are too young (weanlings instead of young adults). The method of incorporation of nicotinamide in the diet (spraying and drying) is not validated. No analysis of the diet was performed to confirm the indicated concentrations.
Reliability	4.

Title	Effects of excess dietary methionine and niacinamide in the rat.
Date of report	1958.
Reference	61.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
GLP	No.
Stat. Method	ANOVA
Method	Nicotinamide was administered to rats in the diet at levels of 0.1, 0.2 and 0.4% (ca. 35, 70 and 140 mg/kg/day) for 12 weeks. Two comparable experiments are reported: In experiment 1 12 male rats (Holtzman, 110-135 g) were used. Animals were weighed weekly. After 2, 8 and 12 weeks 4 animals per group were sacrificed and adrenal glands, liver and kidneys were weighed. In experiment 2 10 rats were used and 5/dose were sacrificed after 8 and 12 weeks. The rest of the procedure was comparable to experiment one.
Results	Nicotinamide at 0.2% caused enhanced growth, while at 0.4% it caused growth inhibition. No effects on organ weights were observed, apart from a statistically significantly decreased relative liver weight after 12 weeks of exposure at 0.2% nicotinamide. This was not a dose dependent effect.
Rev. note	Journal article. Only limited parameters are investigated. Doses in mg/kg/day were calculated by the reviewer, using an average daily food intake of male and female rats (40 and 50 mg/kg/day resp.).
Reliability	4.

Title	Evaluation of the health aspects of niacin and niacinamide as food ingredients.	
Date of report	1979.	
GLP	No.	
Reference	110.	
Test substance	Nicotinamide, purity not indicated.	
Test system	**Species**	Rat; weanling male.
	No. of animals	10/treatment.
	Dosage	Four feeding groups: high fat with or without added nicotinamide (100 mg/kg bw per day) and low fat with or without added nicotinamide (100 mg/kg bw per day).
Results	Increased concentrations of fat in the liver 3 and 6 weeks after instituting the diet were found only when the high fat diet was combined with an excessive intake of nicotinamide. A further study suggested that the fatty livers resulted from an induced choline deficiency brought about by the methylation of nicotinamide to the excretory product N^1-methylnicotinamide.	

Rev. note In an earlier study it is hypothesized that nicotinamide induced a choline deficiency in rats, but not in rabbits and guinea pigs (see also summary ref. 57).
Due to the use of non-standard diet, this study is not comparable to a standard toxicolgical study and is considered less valid.
Reliability 3. Review of FDA.

5.6. Genetic Toxicity

5.6.1. Genetic Toxicity *in vitro*

Title P0080A: Testing for mutagenic activity with *Salmonella typhimurium* TA 1535, TA 1537, TA 1538, TA 98 and TA 100.
Date of report August 1985.
GLP Yes.
Reference 14 .
Test substance CAS 98-92-0 (nicotinamide), purity: 99.9%.
Guideline Not indicated.
Test system
Bacterial strains TA98, TA100, TA1535, TA1537, TA1538.
Deficiency Histidine.
Metabolic activation Rat liver S9 mix (Aroclor 1254-induced).
Test concentration 33, 100, 333, 1000, 3333 and 10000 µg/plate in triplicate with independent repeat.
Controls Negative: vehicle (DMSO).
Positive: sodium azide (TA1535, TA100), 9-aminoacridine (TA1537), 2-nitrofluorene (TA1538, TA98), for all without S9; 2-aminoanthracene, for all strains with S9.
Procedure According to OECD 471; plate incorporation.
Evaluation criteria Response was considered statistically significant mutagenic if a dose-related, reproducible increase (at least a doubling) in number of revertant colonies was observed.

Results

	Test result (A)	
Tester strain	**Without activation**	**With activation**
TA98	-	-
TA100	-	-
TA1535	-	-
TA1537	-	-
TA1538	-	-

(A) +/- : positive/negative result; positive controls gave expected responses.
No precipitation or toxicity was observed.

Conclusion Not mutagenic.
Rev. note The test doesn't contain a strain with an AT basepair at the reversion site, as is recommended in OECD 471 (1997). 2-aminoantracene alone is not considered to be sufficient as positive control for metabolic activation according to OECD 471. It did elicit a positive response, however.
Reliability 1.

Title Mutagenicity evaluation of FDA 75-86 Niacinamide.
Date of report September 1977.
GLP No.
Reference 25.
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline Not indicated.
Test system
Cell type *Salmonella typhimurium* TA1535, TA1537, TA1538, TA100 and TA98.
Deficiencies Histidine.
Metabolic activation With and without.

Metabolic activation sytem Rat, mouse or monkey liver S9 mix.
Test concentrations 0.4, 0.8 and 1.6%.
Controls Negative: solvent treated cells.
Positive (without metabolic activation): Quinacrine Mustard (TA1537), Nitrofluorene (TA1538 and TA98) and methylnitrosoguanidine (TA1535 and TA100).
Positive (with metabolic activation): 2-aminoanthracene (TA1535 and TA100), 2-acetylaminofluorene (TA1538 and TA98) and 8-amino quinoline (TA1537).
Test type Plate incorporation assay.
No. of replicates 2.
Criteria for evaluating results The result was considered positive if a positive dose response (increased number of revertant colonies) was seen over three concentrations with the highest increase equal to two to three times the solvent control.

Results Positive and negative control values were within the expected ranges.
Cytotoxicity: 50% survival at the highest concentration tested.

Test system	Test results[(A)]	
	With activation	Without activation
TA1535	-	-
TA1537	-	-
TA1538	-	-
TA100	-	-
TA98	-	-

(A) +/- : positive/negative result.

Conclusion Not mutagenic.
Rev. note Purity of the test substance is not known.
Only 3 concentrations are tested (OECD 471 recommends at least 5).
In the individual and summary tables, tester strain and/or concentrations are not clearly identified.
Reliability 2.

Title Screening of tobacco smoke constituents for mutagenicity using the Ames' test.
Date of report 1980.
GLP No.
Reference 50.
Test substance CAS 98-92-0 (nicotinamide), purity: >97%.
Guideline Not indicated.
Test system
Bacterial strains TA98, TA100, TA1535, TA1537.
Deficiency Histidine.
Metabolic activation Rat liver S9 mix (Aroclor 1254 or methylcholanthrene induced).
Test concentration 3 µmol/plate (vehicle: ethanol).
Controls Negative: no treatment.
Positive: N-methyl-N'-nitro-N-nitrosoguanidin (without metabolic activation), 2-aminoanthracene (with metabolic activation).
Procedure plate incorporation assay.
Evaluation criteria Increase in the number of revertant colonies was considered a positive result.

Results

Tester strain	Test result [(A)]	
	Without activation	With activation
TA98	-	-
TA100	-	-
TA1535	-	-

TA1537	-	-

(A) +/- : positive/negative result; positive controls gave expected responses.
No precipitation or toxicity was observed.

Conclusion Not mutagenic.
Rev. note Only one concentration is tested.
Journal article.
Only 4 tester strains are used, none of them contains an AT basepair at the reversion site, as is recommended in OECD 471 (1997). As far as can be judged from the limited information, the test substance was amide, not salt.
Reliability 4.

Title Mutagenicity test of food additives with *Salmonella typhimurium* TA97a and TA102.
Date of report 1986.
GLP No data.
Reference 51.
Test substance CAS 98-92-0 (nicotinamide), purity not indicated.
Guideline Not indicated.
Test system
Bacterial strains: TA97a and TA102.
Deficiency: Histidine.
Metabolic activation: S9 mix.
Test concentration: 0, 0.1, 0.5, 1, 5 and 10 mg/plate.
Controls: Negative: vehicle (distilled water).
Positive: 9-aminoacridine (without metabolica activation), 2-aminoanthracene (with metabolic activation).
Procedure: Preincubation assay (20 min.).
Evaluation criteria: Dose dependent increase in the number of revertant colonies.

Results

	Test result [A]	
Tester strain	**Without activation**	**With activation**
TA 97a	-	-
TA102	(+)	-

(A) +/- : positive/negative result; positive controls gave expected responses.
Cytotoxicity was observed at 10 mg/plate in both tester strains with or without metabolic activation.
Controls elicited the expected results.

Conclusion Weakly mutagenic.
Rev. note 1 The report is in Japanese; only the summary and tables could be used, therefore the information is limited. In the summary it was stated that the response was weakly positive in TA102 in absence of metabolic activation. The response was not completely dose-dependent and showed less than a two-fold increase of the recombinant frequency.
2 Only two tester strains are used.
3 Journal article.
Reliability 2.

Title Primary mutagenicity screening of food additives currently used in Japan.
Date of report 1984.
GLP No data.
Reference 65.
Test substance CAS 98-92-0 (Nicotinamide), purity 100%.
Guideline Not indicated.
Test system
Cell type: *Salmonella typhimurium* TA92, TA1535, TA100, TA1537, TA94 and TA98.
Deficiencies: Histidine.
Metabolic activation: With and without.
Metabolic: Rat liver S9 mix (polychlorinated biphenyls induced).

activation sytem
Test concentrations 0-50 mg/plate.
Controls Negative: untreated or solvent (phosphate buffer) treated cells.
Test type Incubation assay; 20 min. at 37 °C.
No. of replicates 2.
Criteria for evaluating results The result was considered positive if the number of revertant colonies found was twice or more that of the control.

Results

Test system	Test results(A)
TA92	-
TA1535	-
TA100	-
TA1537	-
TA94	-
TA98	-

(A) +/- : positive/negative result.

Conclusion Not mutagenic.
Rev. note Only limited information is available on methods and results; the article is a review article of more than 200 investigated substances.
The strains used are no standard strains as recommended by the OECD.
Details on positive controls were not given.
Reliability 2.

Title Mutagenicity evaluation of FDA 75-86 Niacinamide.
Date of report September 1977.
GLP No.
Reference 25.
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline Not indicated.
Test system
Cell types *Saccharomyces cerevisiae* D4 and *Salmonella typhimurium* TA1535, TA1537, TA1538, TA100 and TA98.
Deficiencies Adenine or tryptophane (*Saccharomyces*), histidine (*Salmonella* strains).
Metabolic activation With and without.
Metabolic activation sytem Rat, mouse or monkey liver or lung S9 mix; liver or lung homogenate (for negative controls).
Test concentrations 0.22, 0.44 and 0.88%.
Controls Negative: solvent (saline).
Positive (without metabolic activation): Quinacrine Mustard (TA1537), Nitrofluorene (TA1538 and TA98) and ethylmethanesulfonate (TA1535 and TA100 and D4)
Positive (with metabolic activation): 2-aminoanthracene (TA1538 and TA98), dimethylnitrosamie (TA100, TA1535 and D4) and 8-amino quinoline (TA1537
Test type Pre-incubation assay (48 h for bacteria, 3-5 days for yeasts).
No. of replicates Not indicated.
Criteria for evaluating results Dose related increases in mutants and mutant frequencies.

Results Positive and negative control values were within the expected ranges.
No cytotoxicity or precipitation was observed.

Test system	Test results(A)	
	With activation	**Without activation**
TA1535	-	-
TA1537	-	-
TA1538	-	-

TA100	-	-
TA98	-	-
D4	-	-

(A) +/- : positive/negative result.

Conclusion Not mutagenic.
Rev. note Purity of the test substance is not known.
Only 3 concentrations are tested (OECD 471 recommends at least 5).
In the individual and summary tables, concentrations are not clearly identified.
Reliability 2.

Title Metaphase chromosome analysis of human lymphocytes cultured *in vitro*.
Date of report 8 March 1993.
GLP Yes.
Reference 15.
Test substance CAS 98-92-0 (Nicotinamide), purity 99.9%.
Guideline OECD 473, 1983.
Test system
Cell type Human lymphocytes.
Metabolic activation With and without.
Metabolic activation system Rat liver S9 mix (Aroclor 1254 induced).
Test concentrations Without metabolic activation: 625, 1250, 2500 and 5000 µg/ml
With metabolic activation: 625, 2500 and 5000 µg/ml).
Exposure time 21 or 44 hours (without S9-mix), 3 hours exposure followed by 18 or 41 hours of incubation without test substance (with metabolic activation).
No. of replicates 2.
Controls Positive: ethyl methanesulphonate, mitomycin C (without metabolic activation); cyclophosphamide (with metabolic activation).
Negative: solvent (distilled water).
No. of metaphases analysed 200/treatment.
Criteria for evaluating results The result was considered positive if a statistically significant increase in the number of aberrations was observed, resulting in values above historical control values.
Statistics Fisher's test.
Results
Cytotoxicity MI at 5000 µg/ml without S9-mix: 30-63%; with S9-mix no cytotoxicity was observed.
All controls elicited the expected response.

	Mean no. of aberrations at highest non-toxic dose*	
	Without S9-mix	**With S9-mix**
21 h harvest	0.5	0.5
44 h harvest	1.5**	0.5

* 2500 µg/ml without S9-mix, 5000 µg/ml with S9-mix; data excluding gaps.
** statistically significantly different from control values.

Conclusion Not clastogenic.
Rev. note All values remained within historical control values.
Reliability 1.

Title Benzamide and nicotinamide increase sister chromatid exchanges synergistically with methanesulphonates.
Date of report 1985.
GLP No data.
Reference 31.
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline Not indicated.
Test system Cell type Human peripheral blood lymphocytes.
Metabolic Without.

activation
Test concentration 10^{-3} M, $3x10^{-3}$ M and 10^{-2} M.
Exposure time 72 hours in presence of BrdU (25 µM).
Controls Negative control: no treatment.
No. of metaphases analysed 20.
No. of replicates Not indicated.
Statistics T-test.

Results Ambiguous; reproducibility of the positive response found at 10^{-2} M nicotinamide is not investigated.

Test system	No. of SCE				Test result
	Neg. control	10^{-3} M	$3x10^{-3}$ M	10^{-2} M	
Human blood lymphocytes	7.5	8.2	8.1	12*	+/-

* statistically significant increase

Conclusion Ambiguous.
Rev. note Journal article
No positive controls.
Test substance is not investigated with metabolic activation.
No information on cytotoxicity was provided.
Only 20 metaphases are analysed, while OECD 479 recommends 25.
It is not clear whether the test was conducted with duplicate cultures, as recommended.
Reliability 4.

Title Cytostatic drug activity in plasma, a bioassay for detecting mutagenicity of directly and indirectly acting chemicals, an evaluation of 20 chemicals.
Date of report 1985.
GLP No.
Reference 45
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline Not indicated.
Test system
Cell type Chinese hamster ovary cells (CHO).
Metabolic activation With.
Test concentration 0.3 ml plasma/2 ml medium or 0.5 ml plasma/5 ml medium (plasma of rats receiving 25 mg nicotinamide/kg bw, i.p.).
Exposure time 2 h (0.3/2 ml) or 16 h (0.5/5 ml) (in presence of 5 µM BrdU).
Controls Negative control: solvent (DMSO);
Positive controls: several known indirectly acting mutagens were tested in this system.
No. of metaphases analysed 25-60.
No. of replicates Not indicated.
Procedure Male WAG/RIJ rats (250-340 g) were injected intraperitoneally with 25 mg/kg bw nicotinamide. After 25 min. rats were killed and plasma was collected.
CHO cells were exposed to the plasma, cells were fixed after exposure and for each test concentration 25-60 cells were scored.
Statistics Wilcoxon's and Student's t-test.

Results **Positive.**

Test system	No. of SCE			Test result
	Neg. control	0.3/2	0.5/5	
CHO cells	11.3	15.7	16.8	+

Conclusion Positive.

Rev. note Journal article.
Positive controls gave a positive result.
The positive effect may be attributed to the inhibiting effect of nicotinamide on poly (ADP) ribose synthetase.
Reliability 2.

Title A comparison of the toxic and SCE-inducing effects of inhibitors of ADP-ribosyl transferase in Chinese hamster ovary cells.
Date of report 1984.
GLP No data.
Reference 76.
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline Not indicated.
Test system
Cell type CHO-K_1-BH_4 cells.
Metabolic activation Without.
Test concentration 1, 5, 15 and 17.5 mM.
Exposure time 26 hours at non-toxic concentration (1-5 mM), 46 hours at toxic concentrations (15 or 17.5 mM), in presence of BrdU.
Controls Negative: non-exposed cells.
No. of metaphases analysed 15-25.
No. of replicates 2.

Results

	Concentration of test substance				
	Neg. control	**1 mM**	**5 mM**	**15 mM**	**17.5 mM**
No. of SCE per chromosome	0.6	1	1.3	2.5	2.5
Relative cloning efficiency (%)			100	76	67

It is suggested that nicotinamide increases SCE-frequency by inhibiting ADP-ribosyl transferase, an enzyme demonstrated to be an integral component of DNA repair systems.

Conclusion Positive.
Rev. note Journal article.
No positive controls.
Test substance is not investigated with metabolic activation
According to the author Nicotinamide is thought to excert at least part of its cytotoxic effects through inhibition of ADP-ribosyl transferase (ADPRT). This enzyme is believed to be an integral component of DNA repair systems and to function in the maintenance of normal cellular functions.
Reliability 2.

Title Inhibitors of poly (adenosine diphosphate ribose) polymerase induce sister chromatid exchanges.
Date of report December 31, 1980.
GLP No.
Reference 81.
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline
Test system
Cell type Chinese hamster ovary cells CHO-K1.
Metabolic activation Without.
Test concentration 0.1, 1, 3 and 10 mM.
Controls Negative control.

	No. of metaphases analysed	>40.
	No. of replicates	1.
	BudR concentration	10 µM .
	Procedure	Cells were cultured for the duration of 2 generations in the presence of 5-bromo-2'-deoxyuridine (BudR) and the different concentrations of test substance. Cells were treated with spindle inhibitor (Colcemid) for 2 hours and harvested. Sister Chromatid Exchanges (SCE) were scored under the light microscope. Results were positive if a dose-dependent increase in the number of SCE was seen.
Results		Positive (dose related effect).
Conclusion	Positive.	
Remark	It was suggested that nicotinamide induces SCE by inhibiting poly (ADP-Rib) polymerase.	
Rev. note	Results were not stated by an independent repeat. No duplicate cultures were examined. Substance was not tested with metabolic activation. No SCE numbers are reported; results are only reported as graphs.	
Reliability	2.	

Title	Fanconi's anemia lymphocytes: effect of caffeine, adenosine and niacinamide during G_2 prophase.	
Date of report	1988.	
GLP	No data.	
Reference	82.	
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.	
Guideline	Not indicated.	
Test system	**Cell type**	Peripheral blood lymphocytes of Fanconi's anemia (FA) patients. FA cells show an abnormal sensitivity to the clastogenic effect of DNA cross linking agents and an increased G_2 chromosomal radio sensitivity.
	Metabolic activation	Without.
	Test concentration	3×10^{-4} M.
	Exposure time	2 hours during G_2-prophase.
	Controls	Negative control: no treatment.
	No. of cells analysed	180-280.
	No. of replicates	Not indicated.
	BudR concentration	No indicated .

Results

Test system	**No. of aberrations (%)**	
Concentration	**-**	**$3x10^{-4}$ M**
Patient 1	16.0	4.4
Patient 2	17.6	7.8
Patient 3	48.3	18.5
FA heterozygote 1	2.2	2.2
FA heterozygote 2	3.1	3.5
Normal subject	2.1	12.3

Conclusion	Treatment of FA lymphocytes with nicotinamide caused an improvement in the DNA repair process, probably by increasing the NAD^+ level. In normal subjects, however, nicotinamide appears to be clastogenic.
Rev. note	Only one concentration is tested and analysed. This is not sufficient to establish a dose-response relationship. Journal article. No positive controls. Test substance is not investigated with metabolic activation.

Reliability 4.

Title Induction of sister chromatid exchanges by nicotinamide in Chinese hamster lung fibroblasts and human lymphoblastoid cells.
Date of report 1979.
GLP No.
Reference 97.
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline Not indicated.
Test system
Cell type Chinese hamster fibroblast cells and human lymphoblastoid cells.
Metabolic activation Without.
Test concentration 0, 1, 3.3 and 10 mM (hamster fibroblasts) or 0, 1 and 10 mM (human lymphoblastoids).
Controls Negative control.
No. of metaphases analysed 50 (hamster fibroblasts) or 30 (human lymphoblastoids).
No. of replicates 1.
BudR concentration 3.3 and 33 µM (hamster fibroblasts) or 10 µM (human lymphoblastoids).
Procedure Cells were cultured for the duration of 2 generations in the presence of 5-bromo-2'-deoxyuridine (BudR) and the different concentrations of test substance. Cells were treated with spindle inhibitor (Colcemid) for 2 or 3 hours and harvested. Sister Chromatid Exchanges (SCE) were scored under the light microscope.
Results were positive if a dose-dependent increase in the number of SCE was seen.

Results No cytotoxicity was observed.

Test system	Mean No. of SCE				**Test results**[(A)]
	0 mM	**1 mM**	**3.3 mM**	**10 mM**	
Hamster lung fibroblasts	6.8	10.6	14	19.3	+
Human lymphoblastoids	10	15.3		19.1	+

(A) +/- : positive/negative result.

Conclusion Positive.
Rev. note No duplicate cultures were examined. Results of the test with human lymphocytes were not stated by an independent repeat.
No positive control substance was included.
The substance was not tested with metabolic activation.
For human lymphoblastoid cells only two concentrations were tested.
It cannot be excluded that the mechanism of SCE induction by Nicotinamide may involve inhibition of poly (ADP-ribose) polymerase (leading to activation of endonuclease) or formation of l-methylnicotinamide (using S-adenosyl-L-methionine, leading to disruption of S-adenosyl-L-methionine dependent methylation of cellular macromolecules).
Journal article.
Reliability 2.

Title A comparative analysis of data on the clastogenicity of 951 chemical substances tested in mammalian cell cultures.
Date of report 1988.
GLP No data.
Reference 66.
Test substance CAS 98-92-0 (Nicotinamide), purity not specified.
Guideline Not indicated.
Test system
Cell type Chinese hamster fibroblast, CHL.
Metabolic activation Without
Test concentrations 3000 µg/ml

	Exposure time	48 hours.
Results	Positive; structural and numerical aberrations were observed.	
Conclusion	Clastogenic.	
Rev. note	Only limited information is available on methods and results; the article is a review article of more than 900 investigated substances. The information given in the report is limited to the above mentioned.	
Reliability	4.	

5.6.2. Genetic toxicity, *in vivo*

Title	Nicotinamide: Mouse micronucleus test (single peritoneal administration).	
Date of report	June 30, 1993.	
GLP	Yes.	
Reference	16.	
Test substance	CAS 98-92-0 (Nicotinamide), purity >99% .	
Guideline	OECD 474, 1983.	
Test system	**Species/strain**	Mouse, BOR: NMRI.
	Source	Winkelmann, Versuchtierzucht GmbH & Co.K.G., Borchen.
	No. of animals	Test 1: 18/sex/controls; 21/sex/treatment group. Test 2: 12/sex/control; 14/sex/treatment group.
	Age at study initiation	Test 1: 5 weeks. Test 2: 6 weeks.
	Weight at study initiation	27-34 g (males), 24-29 g (females).
	Test concentration	Test 1: 1470 mg/kg bw. Test 2: 681, 1000 and 1470 mg/kg bw.
	Route of administration	Intraperitoneally (10 ml/kg).
	Controls	Negative control: saline. Positive control: cyclophosphamide.
	Sampling times	Test 1: 24, 48 and 72 hours. Test 2: 48 and 72 hours.
	No. of slides per animal	≥ 2.
	Parameters assessed	Ratio of polychromatic to normochromatic erythrocytes in 1000 erythrocytes. Incidence of micronucleated polychromatic erythrocytes (PCE) per 1000 PCE.
	Criteria for evaluation of results	Test material was considered non-mutagenic if no statistically significant and reproducible positive at any one of the test points was produced, as compared to the negative control group.
	Follow up study	Independent repeat.
	Statistics	Poisson test.
Results		Test 1 found a weakly positive response (males at 48 h), this was not reproduced in the independent repeat experiment.

Test 1

	Negative control	**Positive control**	**Nicotinamide 1470 mg/kg**
Mortality	-	-	-
Clinical signs (A)			+
PCE/NCE ratio	0.8-3.4	0.2-1.9	0.3-2.9
MPCE/1000 PCE at 24/48/72 hours	2.8/3.1/1.6	38.4/16.6/5.5	2.4/5.5/2.6

(A) Clinical signs included hypokinesia, tremor, convulsions, decrease of muscle tone, ptosis, lacrimation, ruffled fur and restrained gait.

Test 2

	Negative control	**Positive control**	**Nicotin-amide 681**	**Nicotin-amide**	**Nicotin-amide**

			mg/kg	1000 mg/kg	1470 mg/kg
Mortality	-	-	-		
Clinical signs (A)			+	+	+
PCE/NCE ratio	1.0-3.4	0.3-1.4	1.3-5.9	0.7-4.1	0.2-3.6
MPCE/1000 PCE at 48/72 hours	2.0/1.8	14/4.1	2.2/2.0	1.7/1.6	4.2/1.7

(A) Clinical signs included hypokinesia, tremor, convulsions, decrease of muscle tone, ptosis, lacrimation, cyanosis and paralysis of hind leg (at 681 mg/kg only slight hypokinesia).

Conclusion Not clastogenic.
Rev. note According to the revised guideline from 1997, 2000 PCE should be scored for the incidence of micronucleated PCE.
Reliability 1.

5.7 Carcinogenicity

Title Pancreatic islet cell tumors produced by the combined action of streptozotocin and nicotinamide.
Date of report 1971.
Reference 83.
Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.
GLP No.
Procedure Male Holtzman rats were treated with a single dose of streptozotocin (50 mg/kg i.v.), with two doses of nicotinamide 350 mg/kg i.p. at 3-hr intervals, or with streptozotocin (50 mg/kg i.v.) and nicotinamide 350 mg/kg i.p. combined. Animals were followed-up for 18 months and at death or sacrifice, pancreatic islet cell tumor incidence was investigated.
Results Streptozotocin treatment caused pancreatic islet cell tumors in 1/26 rats (4%); nicotinamide treatment caused no tumors; combined streptozotocin – nicotinamide treatment caused tumors in 18/28 rats (64%). Treatment had no effect on survival.
Conclusion Treatment with both nicotinamide and streptozotocin resulted in increased incidence of pancreatic cell tumors.
Rev. note Journal article.
Reliability 2.

Title Effect of massive doses of riboflavin, and other vitamins of the B group, on skin carcinogenesis in mice.
Date of report 1962.
Reference 84.
Test substance CAS 98-92-0 (Nicotinamide), purity not inidicated / CAS 59-67-6 (Nicotinic acid), purity not indicated.
GLP No.
Procedure Mice of the 101 strain (10/sex/treatment, 8-10 weeks, mean weight 20.7 g) were given 0.2% nicotinamide (or nicotinic acid) in the drinking water (which corresponds roughly to nicotinamide intakes of 334 mg/kg/day for male mice and 400 mg/kg/day for female mice). They were treated with DMBA (week 4) and croton oil in acetone(15 once-weekly applications from week 7-22) to induce papillomas. Immediately and one month after end of the croton oil treatment, papilloma incidence was investigated.
Results The number of papillomas per survivor of nicotinamide fed rats was 12.1 vs. 10.0 in the control group. The difference in papilloma incidence was not statistically significant.
Conclusion No promoting effect on skin tumors.

Rev. note	It is not clear whether the test substance was nicotinic acid or nicotinamide, due to inconsistencies in the report. Nicotinamide intake was calculated by the reviewer, using estimated mean water intakes of 167 ml/kg/day for male mice and 200 ml/kg/day for female mice. Journal article.
Reliability	4.

Title	Promoting effect of nicotinamide on the development of renal tubular cell tumors in rats initiated with diethylnitrosamine.
Date of report	1985.
Reference	85.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
GLP	No.
Stat. method	T-test, Chi-square test.
Procedure	Male Fischer 344 rats (60 days, mean weight 150 g) underwent partial hepatectomy and were subsequently divided in groups of 10 rats/group. They were pre-treated with diethylnitrosamine (DEN) i.p.. An additional group received 30 mM nicotinamide without DEN-pretreatment. After pre-treatment, animals received, 30 mM or 6.7 mM nicotinamide in the drinking water (corresponding roughly to nicotinamide intakes of 41 and 183 mg/kg/day). Animals were sacrificed after 20 months or when decreased body weight and a palpable mass were detected.
Results	Rats on 30 mM nicotinamide showed statistically significantly reduced growth rate and statistically significantly lower body weights at the end of the experiment. Rats pre-treated with DEN and receiving nicotinamide, at either 6.7 or 30 mM, had a statistically significantly increased dose related renal tumor incidence. Rats on 6.7 mM nicotinamide had a lower renal tumor incidence than rats on 30 mM nicotinamide, but the difference with DEN pre-treated rats not receiving nicotinamide was still statistically significant. Nicotinamide appeared to act as a renal tumor promoter.
Rev. note	Nicotinamide doses in mg/kg/day were calculated by the reviewer, using an estimated water intake for male rats of 50 ml/kg/day and a MW for nicotinamide of 122.13. Journal article. Animals underwent hepatectomy as the studywas intended to investigate hepatic neoplasia.
Reliability	2.

Title	The role of nicotinamide and of certain other modifying factors in diethylnitrosamine carcinogenesis.
Date of report	1977.
Reference	87.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
GLP	No.
Procedure	Rats were pre-treated with nicotinamide and dosed with diethylnitrosamine on the last day of pregnancy and four times during lactation. The animals were kept for at least 7 months after treatment.
Result	Pre-treatment of test animals with nicotinamide can alter the location of tumours induced by diethylnitrosamine. More kidney tumours appeared to develop in the offspring.
Rev. note	Journal article.
Reliability	4.

Title	Lack of carcinogenicity of nicotinamide and isonicotinamide following lifelong administration to mice.
Date of report	1983.
GLP	No.
Reference	94.

Test substance CAS 98-92-0 (nicotinamide), purity 98%.
Guideline Not indicated.
Stat. method Not indicated.
Test system
- Species: Swiss albino mouse (45 days old).
- **No. of animals**: 50/sex.
- **Dosage**: 1% in drinking water, resulting in daily nicotinamide intakes of 2652 mg/kg for females and 3350 mg/kg for males.
- **Exposure period**: Lifelong exposure.
- **Observations**: Water consumption (fixed intervals), clinical signs and body weight (weekly).
- **Necropsy**: Macroscopy of all organs; histological examination of liver, spleen, kidneys, bladder, thyroid, heart, testes, pancreas, ovaries, brain, nasal turbinals, at least 4 lobes of the lungs and organs showing gross pathological changes.

Results

Treatment	Tumour incidence (%)		
	Lung	Lymphoma	Blood vessels
Control (females)	15	20	8
Control (males)	22	8	5
2652 mg/kg NA (females)	14	18	2
3350 mg/kg NA (males)	12	8	6

Mortality: Treatment had no statistically significant effect on survival of the animals.

Conclusion Not carcinogenic under present experimental conditions.
Rev. note Journal article; the information presented was limited to the above mentioned.
Only one dose level was investigated.
Fresh water 3 times weekly but no stability data for the test substance in water are presented.
NA doses in mg/kg bw/day were calculated by the reviewer, using an average body weight of 30 g for male mice and 25 g for female mice. Daily NA intake was reported to be 100.5 and 66.3 mg.
Reliability 2.

Title Inhibiting effects of nicotinamide on urethane-induced malformations and tumors in mice
Date of report 1988.
GLP No data.
Reference 55.
Test substance CAS 98-92-0, Nicotinamide, purity not indicated.
Guideline Not applicable.
Stat. method Not indicated
Test system
- Species: CL/Fr mouse, females, 28 weeks.
- **No. of animals**: Not indicated.
- **Dosage**: 0.5, 1.0 and 2.5% in diet
- **Procedures**: Mice received urethane (single dose 1000 mg/kg bw s.c.) followed by nicotinamide for 10 days and were sacrificed 5 months after urethane treatment.
Gross pathology, especially tumours were examined. Frequency of nodules in the lung was established

Results

Effect	Dose (in diet)			
	control	0.5%	1.0%	2.5%
Lung tumour bearing mice	27/31	Not reported	47/51	47/54
No. tumours/lung	20	Not reported	13	7

Conclusion Nicotinamide reduced the number of lung tumours

Rev. note The information is essentially confined to the above mentioned.
Reliability 2

Title Niacinamide and Niacin, CIR report, scientific literature review, 2001.
Date of report 2001.
Reference 113.
Test substance CAS 98-92-0, Nicotinamide, purity not indicated.
GLP No.
Method Syrian golden hamsters (number not indicated) were treated with
Group 1 N-nitrosobis(2-oxopropylamine) 10 mg/kg bw s.c.,
Group 2 N-nitrosobis(2-oxopropylamine) 10 mg/kg bw s.c. with nicotinamide i.p. (350 mg/kg bw) 5 minutes before and 3 hours after s.c. treatment,
Group 3 2x nicotinamide i.p. (350 mg/kg bw) 3 hours apart
Group 4 saline control
Animals were sacrified after 52 weeks and necropsied completely.
Results In group 1 5/60 animals developed ductal-ductular carcinomas. In the other groups no ductal-ductular carcinomas were observed.
Conclusion Nicotinamide inhibits the induction of ductal-ductular adenomas by N-nitrosobis(2-oxopropylamine)
Rev. note Review paper
Reliability 4.

5.8 Reproductive Toxicity

Title P0076 : Teratology study in the rat.
Date of report 1992.
GLP Yes.
Reference 20.
Test substance Nicotinic acid, purity 99.8%.
Guideline FDA (1964), EEC (1983).
Stat. method Nested analysis of variance
Test system
Species Rat (CD, Sprague-Dawley), females, age 10-11 weeks, weight 222-269 g.
Source Charles River, UK.
No. of animals 22/treatment.
Dosage 40, 200 and 1000 mg/kg bw daily from day 6-15 of gestation by oral gavage; vehicle controls (aqueous methylcellulose (0.5%)); dosing volume 10 mL/kg.
Analyses Accuracy of preparation during week 1 and 2; stability (48 h) and homogeneity during a preliminary study.
Observations Females were mated with fertile males (1/1). The day of detection of sperm or at least 3 vaginal plugs was designated day 0 of gestation. Mortality/clinical signs of dams were noted daily. Body weights were recorded on day 0, 3, 6-16, 18 and 20 of gestation. Food/water consumption was recorded on day 2, 5, 9, 12, 15 and 19. All females were killed on day 20 of gestation and subjected to macroscopic examination. The reproductive tract (incl. ovaries) was dissected and examined for number of corpora lutea, implantations, early and late resorptions and foetuses. Foetuses were weighed, sexed and examined for external (all), internal (1/2), visceral (1/2) and skeletal (1/2) abnormalities. Placenta weights were determined.

Results
Analyses Concentrations 93-100% of nominal; homogeneity 82-114%; stability 98-104%.

Dose (mg/kg bw)	0	40	200	1000	DR
Maternal					
Mortality	None				
Clinical signs	No treatment related effects				

Body weight gain				d	
Food/water consumption	No treatment related effects				
Macroscopy	No treatment related effects				
Number of pregnancies	22	22	22	22	
Corpora lutea/implantation sites	17.6/15.7	17.4/16.0	16.5/15.3	16.7/15.7	
Post implantation loss (%)	4.6	6.0	5.7	4.9	
Resorptions early	0.7	1.0	0.9	0.7	
late	0	0	0	0.05	
Placental weight				dc	
Foetal					
Number of litters evaluated	22	22	22	22	
Number of live foetuses	15	15	14	15	
Sex	No treatment related effects				
Weight				dc*	
External/internal/ visceral/ skeletal abnormalities	No treatment related effects				

* males only

Conclusion NOAEL for maternal effects 200 mg/kg bw based on slightly reduced body weights.
NOAEL for reproductive effects 200 mg/kg bw based on decreased placental weights and decreased foetal weights in males.
Not teratogenic.

Rev. note The test substance nicotinic acid. The metabolism of the acid may be quantitatively different from that from the amide (ref 74).

Reliability 1.

Title Inhibiting effects of nicotinamide on urethane-induced malformations and tumors in mice

Date of report 1988.

GLP No data.

Reference 55.

Test substance CAS 98-92-0, Nicotinamide ([carbonyl-^{14}C]nicotinamide), purity not indicated.

Guideline Not applicable.

Stat. method Not applicable.

Test system

Species	CL/Fr mouse, age 8-10 weeks
No. of animals	Not indicated.
Dosage	0.5 mg/g bw i.p. daily or 0.5 and 1.0% in diet
Procedures	Pregnant mice received nicotinamide from day 7 to 10 of gestation and were sacrificed on day 17. Number of pregnancies, implants, resorptions and living foetuses were determined. Gross anomalies (cleft lips and palates) were examined.

Results

Effect	**Dose**			
	control	**0.5%**	**1.0%**	**0.5 mg/g bw**
No. of pregnancies	31	16	14	N/A
Mean no. of Implantation sites	8.6	8.3	8.8	N/A
Mean no. of early resorptions	0.5	0.8	0.6	N/A
Mean no. of late resorptions	1.1	0.8	1.0	N/A
Mean no. of live foetuses	7.0	7.1	6.8	N/A (total 81)
% Malformations	30	18	28	26

Conclusion Not clear evidence of antiteratogenic effect on the spontaneous malformations because of not consistent dose related response.

Rev. note The strain of mice used is known to develop about 30% spontaneous malformations. In a separate test urethane-induced malformations were reduced by treatment with nicotinamide, but not by treatment with nicotinic acid.
Reliability 2.

Title Inhibiting effects of nicotinamide on urethane-induced malformations and tumors in mice
Date of report 1988.
GLP No data.
Reference 55.
Test substance CAS 98-92-0, Nicotinamide, purity not indicated.
Guideline Not applicable.
Stat. method Not applicable.
Test system
Species CL/Fr mouse, age 8-10 weeks
No. of animals Not indicated.
Procedures Pregnant mice received a single injection of urethane (1000 mg/kg bw s.c.) on day 9 of gestation. Thereafter animals received nicotinamide by several applications routes and schedules and were sacrificed on day 18 (see scheme). Controls received urethane only or nicotinamide treatment only.
Number of pregnancies, implants, resorptions and living foetuses were determined. Gross anomalies (cleft lips and palates) and skeletal malformations were examined.
Treatment scheme At 0, 24 and 48 h after urethane treatment 5 times (frequency 6 hours) nicotinamide i.p. at 0.5 mg/kg bw (at 0 h also 0.1 or 0.3 mg/kg bw 5 times)
In diet at 0.5, 1.0, 3.0 and 5.0% from 0-48 hours after urethane treatment

Results

Effect	**Dose (mg/kg bw)**			
	control	**0.1**	**0.3**	**0.5**
Nicotinamide i.p.				
No. pregnancies	18	17	18	18
Malformations	65%	45%*	30%*	23%*
Effect	**Treatment (h)**			
	control	**0-24**	**24-48**	**48-72**
Nicotinamide i.p.				
No. of pregnancies	18	18	19	15
Malformations	65%	20%*	35%*	58%*

Effect	**Dose (% in diet)**				
	0	**0.5**	**1.0**	**3.0**	**5.0**
Nicotinamide diet					
No. of pregnancies	18	19	19	12	11
Malformations	65%	38%*	25%*	42%*	44%

*Statistically significant effect

Conclusion Evidence of antiteratogenic effect on the urethane induced malformations, but no consistent dose related response.
Rev. note The strain of mice used is known to develop about 30% spontaneous malformations.
Reliability 2.

5.9 Other relevant Information

Title Effects of nitrogen compounds with hexobarbital induced sleep in Swiss albino mice.
Date of report 1991.
Reference 26.
GLP No data.

Remark	Nicotinamide was administered intraperitoneally to female mice 30 min. prior to hexobarbital administration (75 mg/kg i.p.). Doses applied were 485, 970 and 1940 mg/kg bw. At 970 and 1970 mg/kg sleeping time was statistically significantly increased, while at 485 mg/kg no effect was seen. It was suggested that nicotinamide prolongs the metabolisme of hexobarbital by inhibition of the cytochrome P-450 dependent microsomal mixed-function oxidase system in the liver.
Rev. note	Journal article
Reliability	2.

Title	Effect of nicotinamide on drug metabolising enzymes in the neonatal rat.
Date of report	1987.
Reference	28.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
GLP	No data.
Stat. methods	Oneway ANOVA, Student Neuman Keuls procedure and linear regression.
Procedure	Whole litters of 4-day old Sprague-Dawley rats were artificially (through a gastric cannula, fitted under anesthesia) fed the following diets for 7 days: control, nicotinamide 300 mg/L diet, 750 mg/L diet and 1500 mg/L diet). Treatment resulted in nicotinamide intakes of 26-38, 120-165, 255-378 and 477-747 mg/kg/day for mentioned groups resp. throughout the study period. Body weights of the pups were measured at day 4, 7 and 11 of age. Pups were killed on day 11 of age, livers were weighed and liver microsomes were isolated for measurement of uridine diphosphoglucuronyl transferase (UDPGT-PNP) activity, cytochrome P-450 content and microsomal protein content.
Results	The only effect found was a dose-dependent increase in UDPGT-PNP activity, with a statistically significantly increased value at the highest dose level. All other parameters measured were within the same ranges as the artificially fed controls.
Rev. note	Journal article Only limited parameters are investigated. No data are reported on group composition (number of animals, sex). Control animals (artificial reared) had some nicotinamide intake through a vitamin supplement and evaporated whole milk in the control diet, and were compared with mother reared animals.
Reliability	4.

Title	Pharmacologic effects of nicotinic acid on human purine metabolism.
Date of report	1974.
Reference	52.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
GLP	No.
Method	Nicotinamide was administered orally to 3 patients at a dosage of 1 g. During 6 h after administration, blood samples were collected hourly for measurement of uric acid, creatinine and erythrocyte phosphoribosyltransferases. Urine samples were collected every 2 hours for determination of uric acid, oxyprine and creatinine.
Results	Four to six hours after ingestion, nicotinamide caused a minimal diminution (ca. 15%) in the fractional uric acid clearance compared to pre-test values; four hours after ingestion a 34% decrease in erythrocyte phosphoribosylpyrophosphate (PRPP) concentration was seen. Other parameters were not reported.
Rev. note	Journal article. Nicotinamide may influence *de novo* purine biosynthesis by the influence of NADP on the synthesis of PRPP, controlling the availability of ribose-5-phosphate (hexosemonosphosphate shunt).
Reliability	4.

Title	The pharmacological effects of massive doses of nicotinamide.

Date of report	1953.
Reference	39.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
GLP	No.
Remark	Nicotinamide was administered to dogs, cats and rabbits to investigate the effects on blood pressure, respiration and heart rate. 500-1000 mg/kg was administered intravenously. Blood pressure showed a sudden fall within less than a minute and returned to normal after 10-20 minutes. In cats little change in heart rate was observed, while in dogs marked tachycardia was observed. Respiratory movements may stop for the first few seconds after exposure and continue with increased depth and sometimes increased frequency, so that pulmonary ventilation is always increased. Blood pressure and respiratory effects were also obtained after intraperitoneal administration, although less pronounced. Nicotinamide was administered to rabbits and rats to investigate the effect on blood sugar. Dose levels were 750 mg/kg i.v. (rabbits), 1000 mg/kg i.p. (rats and rabbits), 2000 mg/kg orally (rabbits) or 750 mg/kg s.c.. Two rabbits and four rats were used per treatment. Administration of nicotinamide caused hyperglycemia at all dose levels in both rabbits and rats, regardless of the route of administration (maximum level 1-1.5 h after administration). Intravenous administration of nicotinamide to dogs caused degenerative changes in the liver with vacuolisation both in the peripheral and central parts of the lobules. Intraperitoneal administration of nicotinamide (500-1000 mg/kg) to rats (4/dose level) caused oliguria with an almost complete suppression of urine excretion at 1000 mg/kg. Histopathological examination of the kidneys (after mercurial induced diuresis and subsequent nicotinamide administration) revealed swollen tubular epithelium and hydrophic degeneration of the cells lining the collecting tubules; the interstitium tissue showed oedema. Administration of 250 mg/kg had no effect on urine excretion. Nicotinamide was administered intraperitoneally to rats at dose levels of 750 and 1000 mg/kg. Nicotinamide excretion in the urine of the rats returned to normal about 12 hours after administration. Nicotinamide is distributed very rapidly throughout the extra-cellular fluid. However, 3-4 hours pass by before the blood concentration sinks below detection level (after intravenous administration). Nicotinamide can be removed from the blood by the kidneys or pass into the intracellular space. This latter process appears to be rather slow and is probably dependent on an enzymatic reaction.
Rev. note	Review article.
Reliability	4.

Title	Nicotinic acid.
Date of report	1990.
GLP	Not applicable.
Reference	54.
Test substance	Not applicable.
Guideline	Not applicable.
Findings	Nicotinic acid and nicotinamide are identical in their function as vitamins, but differ markedly as pharmacological agents. Both are readily absorbed from the GI-tract. At

low doses small amounts of the unchanged vitamin appear in urine, at high doses the unchanged vitamin is the major urinary component. The principle metabolite is N-methylnicotinamide.
Nicotinamide is used in prophylaxis and treatment of pellagra.

Rev. note No clear distinction between the acid and the amide was made. Pharmacological differences were not elucidated.

Conclusion Nicotinic acid and nicotinamide differ pharmacologically.

Reliability 4.

Title Radiosensitization by nicotinamide *in vivo*: A greater enhancement of tumor damage compared to that of normal tissues.

Date of report 1987.

GLP No data.

Reference 62.

Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.

Guideline Not applicable.

Stat. method Probit analysis

Test system

Species	3-month-old female BALB/c, C3H/K and C57BL/6 mice, inoculation with solid tumours (EMT6, RIF-1 and Lewis lung, respectively).
No. of animals	Not indicated
Dosage	i.p. injection at 1000 mg/kg bw; saline controls Irradiation when tumor size 100-300 mg.
Observations	Nicotinamide concentration in prepared plasma and tumour samples by HPLC with UV-detection at 265 nm.

Results 1. Nicotinamide level (EMT6):
Plasma: $C_{max} \cong 8$ mM (1 mg/ml) reached at 30-60 min. after injection; $T_{1/2} = 2.9 \pm 0.3$ h.
Tumour: $C_{max} \cong 7$ mM reached at 30-60 min. after injection; $T_{1/2} = 3.1 \pm 0.3$ h.
2. In all 3 tumor models nicotinamide produced a slop modification of the X-ray survival curve (P values significant different with the t test)

Conclusion Nicotinamide enhanced the radiation-induced cell killing in 3 different tumour models when injected at least 1h before irradiation.

Rev. note The information was essentially confined to the above mentioned.

Reliability 2.

Title Pancreatic islet cell tumors produced by the combined action of streptozotocin and nicotinamide.

Date of report 1971.

Reference 83.

Test substance CAS 98-92-0 (Nicotinamide), purity not indicated.

GLP No.

Procedure Male Holtzman rats were treated with a single dose of streptozotocin (50 mg/kg i.v.), with two doses of nicotinamide 350 mg/kg i.p. at 3-hr intervals, or with streptozotocin (50 mg/kg i.v.) and nicotinamide 350 mg/kg i.p. combined. Animals were followed-up for 18 months and at death or sacrifice, pancreatic islet cell tumor incidence was investigated.

Results Streptozotocin treatment caused pancreatic islet cell tumors in 1/26 rats (4%); nicotinamide treatment caused no tumors; combined streptozotocin – nicotinamide treatment caused tumors in 18/28 rats (64%). Treatment had no effect on survival.

Conclusion Treatment with both nicotinamide and streptozotocin resulted in increased incidence of pancreatic cell tumors.

Rev. note Journal article.

Reliability 2.

Title Mechanism of conversion of extracellular niacinamide to niacin by *Escherichia coli.*

Date of report 1972.

Reference 108.

Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
GLP	No.
Remark	Cell-free extracts of *Escherichia coli* convert nicotinamide to nicotinic acid by an amidase. In cell-free growth medium, this conversion did not take place, which indicates that the enzyme is located within the bacterial cell. Most of the nicotinic acid formed is excreted. The nicotinamidase has a high substrate affinity and there is no product inhibition. The enzyme also appears not inducible. It is suggested that nicotinamide is taken up by *E. coli* in the intestine, metabolised to nicotinic acid and subsequently excreted, before it is utilized by the human body.
Rev. note	Journal article.
Reliability	4.

Title	Evaluation of the health aspects of niacin and niacinamide as food ingredients.
Date of report	1979.
Reference	110.
Remark	Review of FDA covering background information, exposure data, biological studies and opinions. Nicotinic acid is readily converted in the body to the physiologically active nicotinamide. In the older literature niacin = nicotinic acid, but more recent papers use the term niacin to denote nicotinic acid and its derivatives exhibiting qualitatively the biological activity of nicotinamide. The Recommended Dietary Allowance for adults is 6.6 mg niacin per 1000 kcal, with not less than 13 mg daily. Nicotinamide is much more soluble than nicotinic acid in water (1g/ml compared to 1g/60 ml). Nicotinic acid or nicotinamide is used to enrich various foods such as bakery, cereal, and pasta products. Nicotinic acid is known to decrease serum concentrations of lipids in some patients with hyperlipoproteinemia. Both nicotinic acid and nicotinamide have been used in treatment of schizophrenia. The main metabolites are N^1-methyl-nicotinamide and N^1-methyl-2-pyridone-5-carboxyamide. Minor metabolites are N^1-methyl-4-pyridone-3-carboxyamide and nicotinamide-N-oxide.
Reliability	4

Title	Safety of high-dose nicotinamide: a review
Date of report	2000
Reference	119
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
GLP	Not applicable
Remark	Potential toxic effects in animals: 0.5% supplementation in diet: increased liver fatty acid contents 1% supplementation in diet: growth retardation possible coteratogenic/antiteratogenic effects in chick embryos (at 2.5 and 19 mg/egg resp.) In rodents at 350 mg/kg bw and 1% in drinking water no carcinogenic action. When applied (305-500 mg/kg bw) together with streptozotocin and alloxan development of pancreatic islet cell tumours Potential effects in humans: Liver toxicity: jaundice (one reference)
Reliability	2.

5.10 Experience with Human Exposure

Title	The file of side effects to the skin: a guide to drug eruptions
Date of report	1989.
Reference	42.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
Procedure	Human exposure
Results	Unexpected therapeutic effect on Necrobiosis lipoidica.
Rev. note	Journal article.
Reliability	4.

Title	Pruritus associated with nicotinamide (letter to the editor).
Date of report	1980.
Reference	44.
Test substance	CAS 98-92-0 (Formulation containing nicotinamide), purity not indicated.
GLP	Not applicable.
Remark	A 71-year old man suffered from reproducible itching pruritus on his neck and shoulders, presumably caused by nicotinamide. The patient had been taking a megavitamin containing 100 mg of nicotinamide.
Rev. note	Secondary literature (letter to the editor).
Reliability	4.

Title	Administration of nicotinamide during CHART: pharmacokinetics, dose escalation, and clinical toxicity.
Date of report	1995.
GLP	No data.
Reference	64.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline	Not applicable.
Stat. method	Not applicable.
Test system	Human patients aged 54-82 undergoing accelerated cancer radiotherapy (CHART regimen) were given a dose of nicotinamide as radio-sensitizer with the second fraction of radiotherapy each day over 12 consecutive days. Doses of ~80, 90, 100 mg/kg bw were administered to 7, 2 and 2 patients, respectively. Sampling times for 80 mg/kg bw: day 1, 4, 8 and 11 at most.
Results	*Pharmacokinetic profile*: T_{max} = 0.8-4 h; C_{max} = 0.5-1.4 µmol/ml; $t_{1/2}$ = 7.1 h (dose = 80 mg/kg bw) and 8.6 h (dose = 90-100 mg/kg bw). A dose of 80 mg/kg bw showed no statistically significant drug accumulation, but the higher doses did. *Toxic effects*: A dose of 80 mg/kg bw resulted only in mild to moderate clinical symptoms (headache, anorexia, itching, insomnia, nausea), but the higher doses gave severe nausea with vomiting and dizziness (none of the 4 patients completed the planned administration). One patient was found with a cardiovascular collapse after severe hypotension (ischemic ECG).
Rev. note	Journal article.
Reliability	2.

Title	Administration of nicotinamide during a five- to seven-week course of radiotherapy: pharmacokinetics, tolerance, and compliance.
Date of report	1997.
GLP	No data.
Reference	69.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
Guideline	Not applicable.
Stat. method	Not applicable.

Test system	40 human head and neck cancer patients were administered orally nicotinamide (80 mg/kg bw to a max. of 6 g/day) dissolved in fruit juice 1-1.5 h before irradiation, daily during a 5- to 7-week course of radiotherapy. Nine patients were treated by conventional schedule and 31 by an accelerated fractionation schedule. Sampling times: 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 12 and 24 h after first nicotinamide ingestion; 1-1.5 h after second dose of nicotinamide; thereafter, daily during the first and last full weeks of treatment 1-1.5 h after nicotinamide intake.
Results	In all patients peak concentrations > 700 nmol/ml could be achieved 0.25-3 h after drug intake. At the start of the treatment 82% of the measured values were above the desired 700 nm/ml, while towards the end of the treatment only 59% of the values were above the desired level. High plasma concentrations over subsequent days are associated with severe side-effects, whereas daily dose was not (systemic effect). The most important side-effect was nausea with or without vomiting occurring in 65% of the patients. No effect on blood pressure was observed. Tolerance improved after a reduction of the dose with 25% in six of seven patients. A liquid formulation produced higher peak levels than tablets used in other studies and also a shorter T_{max}: 0.83±0.73 h as compared to 2.1±1.3 h with tablets.
Conclusion	C_{max} = 752-2041 nmol/ml T_{max} = 0.25-3 h.
Rev. note	Journal article.
Reliability	2.

Title	Hepatic toxicity from large doses of vitamin B_3 (nicotinamide).
Date of report	1973.
Reference	101.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
GLP	No.
Findings	A case is reported of a 35-year old subject, who took nicotinamide (3g/day) for schizophrenia treatment. He had a 6-month history of nausea and vomiting during which he had been hospitalised two times. SGOT, SGPT and billirubin were increased and prothrombin time was prolonged. Liver biopsy showed an increase in portal fibrosis with sparse portal inflammatory infiltrate and mild proliferation of bile ductules. Centrilobular parenchymal cells were swollen and the cytoplasm was vacuolated. A few mitotic figures and a number of canalicular bile plugs were present. There was no cell necrosis.He was diagnosed with hepatitis. Tests for viral infection were negative. Symptoms disappeared upon discontinuation of nicotinamide. It was discovered and acknowledged that the subject had increased the dose of nicotinamide to 9 g/day several days prior to each episode of nausea and vomiting.
Rev. Note	Journal article.
Reliability	4.

Title	Nicotinamide-induced hepatic microsomal mixed function oxidase system in rats.	
Date of report	1980.	
GLP	No data.	
Reference	70.	
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.	
Guideline	Not applicable.	
Stat. method	Not applicable.	
Test system	**Species**	Rat (Wistar), males/females, body weight 150-200 g.
	Experiment 1	*Dosage*: Single i.p. administration of 50 and 100 mg/kg bw for males and 250 and 500 mg/kg bw for females. *Observation*: Hepatic NADPH-cytochrome *c* reductase activity was determined in rat microsomal fractions at various intervals up to 48 h.
	Experiment 2	*Dosage*: Single i.p. administration of 100 mg/kg bw to 8-12 male rats; 10-15 control rats. *Observation*: levels of cytochrome *P*-450 and cytochrome b_5 and incorporation of DL-[1-^{14}C]leucine 24 h after treatment.

	Experiment 3	*Dosage*: Single i.p. administration (probably 100 mg/kg bw) to 10-15 male rats; 10-15 control rats. *Observation*: Hepatic microsomal activities of UDP-glucuronosyl-transferase, arylhydrocarbon hydroxylase and aminopyrine demethylase 24 h after treatment.
Results	**Experiment 1**	Optimal induction (ca. 100%) of NADPH-cytochrome *c* reductase is obtained at 24 h after administration at a dose of 100 mg/kg bw for males and 250 and 500 mg/kg bw for females; higher doses were needed for females.
	Experiment 2	An induction of 70% was observed for cytochrome b_5 and cytochrome *P*-450 relative to the control group. An increase of 91% in incorporation of DL-[1-^{14}C]leucine into hepatic microsomal proteins was observed relative to the control group.
	Experiment 3	UDP-glucuronosyl-transferase, arylhydrocarbon hydroxylase and aminopyrine demethylase activity were increased by 76, 120 and 88% relative to the control group, respectively, following nicotinamide administration.
Conclusion	Nicotinamide was shown to induce the activity of mixed function oxidases in rats.	
Rev. note	Individual data of animals not reported.	
Reliability	2.	

Title	Reactions to niacinamide (letter to the editor).
Date of report	1981.
Reference	102.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated or CAS 59-67-6 (Nicotinic acid), purity not indicated.
GLP	Not applicable.
Findings	Psoriasis patients were treated with 6-aminonicotinamide (topical) and nicotinamide (oral) (500-1000 mg t.i.d). Of 204 patients 8 developed adverse reactions consisting of flushing, facial erythema, mild nausea or dull headache. It cannot be excluded that some of the patients received nicotinic acid instead of nicotinamide. Treatment of schizophrenics (both adults and children) with nicotinamide in doses up to 12 g per day did not cause severe side effects. Incidental cases of among other things gastrointestinal complications, headaches and heartburn were reported. Incidental cases of hepatotoxicity are reported for nicotinamide or nicotinic acid: one patient suffered from obstructive jaundice following treatment (dose not stated) and a 35-year old man developed reproducible hepatotoxicity following a daily dose of 9 g nicotinamide (see ref. 101).
Rev. note	Secondary literature (letter to the editor). In most cases it was not clear if the patients actually received nicotinamide or nicotinic acid.
Reliability	4.

Title	Nicotinamide and diabetes prevention.
Date of report	1995.
Reference	36.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
GLP	No data.

Procedures	Nicotinamide can prevent the onset of Insulin Dependent Diabetes Mellitus (IDDM). A population-based intervention trial on 20,195 children aged 5-7.9 years found a 50% reduction in development of IDDM within 5 years for children at increased risk (n=150) treated with nicotinamide (1.2 g/m^2 body surface/day) compared to non-treated children. Increased risk of IDDM was defined as presence of islet cell antibodies in the blood. The mechanism of this prevention is not clear. It might be attributed to the inhibition of poly(ADP-ribose) synthetase or prevention of NAD^+ depletion, protecting islet cells from free radical damage.
Rev. note	Review article.
Reliability	4.

Title	Safety issues regarding the use of vitamin supplements.
Date of report	1992.
GLP	Not applicable.
Reference	38.
Test substance	Not applicable.
Guideline	Not applicable.
Stat. method	Not applicable.
Findings	Niacin includes nicotinic acid and nicotinamide. Nicotinic acid, but not nicotinamide, has been successfully used to lower serum cholesterol levels. Liver damage is a realistic problem.
Rev. note	Although niacin is the subject, no safety issues are reported about nicotinamide.
Reliability	4.

Title	Nicotinsäure ind Nicotinamid (letter from IVDK)
Date of report	1997.
Reference	116.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
GLP	No.
Result	No cases of contact allergy after nicotinamide are known in the German “Allergenkatalog”.
Reliability	4.

Title	Double blind trial of nicotinamide in recent-onset IDDM (the IMDIAB III study),
Date of report	1995
Reference	120.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
GLP	Not applicable
Procedures	Patients with recent-onset insulin-dependent diabetes received 25 mg/kg bw nicotinamide daily for 12 months (n=28) or placebo (n=28) in addition to 3-4 insulin injections daily. Parameters investigated were glycated haemoglobin and C-peptide secretion. Drug toxicity was evaluated by liver and renal function tests.
Results	Nicotinamide preserved and improved beta-cell function in patients diagnosed after puberty. No adverse effects were observed in patients taking nicotinamide
Reliability	2.

Title	The Deutsche Nicotinamide Intervention Study
Date of report	1998
Reference	121.
Test substance	CAS 98-92-0 (Nicotinamide), purity not indicated.
GLP	Not applicable

Procedures	Children (age 3-12) of patients with insulin-dependent diabetes, which were diagnosed to be at risk of developping insulin-dependent diabetes were treated with 1.2 g nicotinamide/m^2 body surface/ day (n=25) or placebo (n=30) during maxiumum 3.8 years.
Results	The trial was terminated as it was concluded that a reduction of the cumulative diabetes incidence at 3 years was not achieved. No side effects of nicotinamide treatment were observed.
Reliability	2.

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