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N-Ethylretinamide

1. Chemical and Physical Characteristics

1.1 Nomenclature

See General Remarks, Section 1.4

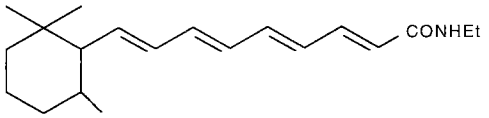
1.2 Name

Chemical Abstracts Services Registry Number
33631-41-3

IUPAC Systematic name
N-Ethyl (2E,4E,6E,8E)-3,7-dimethyl-9-(2,2,6-trimethylcyclohexenyl)-2,4,6,8-nonatetraenamide

Synonyms
all-*trans*-*N*-Ethylretinamide, NER, *N*-ethyl all-*trans*-retinamide, *N*-ethyl (E)-3,7-dimethyl-9-(2,2,6-trimethylcyclohexenyl)-2,4,6,8-nonatetraenamide, *N*-ethyl retinamide, Ro 8-4968.

1.3 Structural formula



Composition: $C_{22}H_{33}NO$
Relative molecular mass: 326.3

1.4 Physical and chemical properties

Description
Pale-yellow crystals

Melting-point
137–138 °C

Spectroscopy
UV and visible: λ_{max} 347 nm; $E^{1\%}_{1\,cm}$ 1540 (Bollag *et al.*, 1976); λ_{max} (ethanol) 347 nm (ε = 50 300 M^{-1} cm^{-1}) (Zanotti *et al.*, 1993).

Solubility
Soluble in organic solvents

Stability
Unstable to light, oxygen and heat

2. Occurrence, Production, Use, Human Exposure and Analysis

2.1 Occurrence

N-Ethylretinamide, a synthetic compound, is not present in food, and human exposure is limited to medical treatment.

2.2 Production

N-Ethylretinamide is prepared by treatment of an etheral solution of all-*trans*-retinoyl chloride with ethylamine at 0 °C, followed by room temperature for 4 h and reflux temperature for 2 h (Bollag *et al.*, 1976). The acid chloride is prepared by treatment of all-*trans*-retinoic acid with thionyl chloride. The compound became available from the United States National Cancer Institute Chemical Repository in 1998.

2.3 Use

N-Ethylretinamide has not been used extensively in humans.

2.4 Human exposure

N-Ethylretinamide has been used in some trials for psoriasis (Runne *et al.*, 1973).

2.5 Analysis

N-Ethylretinamide can be separated by reversed-phase high-performance liquid chromatography and quantified by its ultraviolet absorption at 347 nm (Shih *et al.*, 1988).

3. Metabolism, Kinetics and Genetic Variation

3.1 Humans

No data were available to the Working Group.

3.2 Experimental models

Enzymatic activity present in rat liver microsomes hydrolysed *N*-ethylretinamide to all-*trans*-retinoic acid. The reaction was more rapid than that for 4-hydroxyphenylretinamide (Shih *et al.*, 1988).

4. Cancer-preventive Effects

4.1 Humans

No data were available to the Working Group.

4.2 Experimental models

4.2.1 Cancer and preneoplastic lesions

These studies are summarized in Table 1.

4.2.1.1 Trachea

Hamster: Groups of 63 male Syrian hamsters were given intratracheal instillations of *N*-methyl-*N*-nitrosourea (MNU), [amount not stated] once a week for 12 weeks and one week after the last exposure were placed on diets containing *N*-ethylretinamide at 1 mmol/kg of diet (327 mg/kg of diet) for six months, at which time they were killed and examined for tracheal neoplasms. None of 12 hamsters given only *N*-ethylretinamide developed an epithelial neoplasm, but of the animals dosed with MNU and fed a control diet, 16% developed epithelial neoplasms and 6% had carcinomas. Of hamsters dosed with MNU and fed the diet containing *N*-ethylretinamide, 38% developed epithelial neoplasms and 19% had carcinomas. The incidence of epithelial neoplasms and carcinomas in *N*-ethylretinamide-treated hamsters was significantly greater than that in controls ($p < 0.01$ and < 0.05, respectively; χ^2 test; Stinson *et al.*, 1981).

4.2.1.2 Liver

Mouse: Groups of 25–29 B6D2F1 mice were given a single intraperitoneal injection of *N*-nitrosodiethylamine (NDEA) at 50 or 100 mg/kg bw and one week later were fed a diet containing *N*-ethylretinamide at 0.5 or 1 mmol/kg of diet for 12 months. In mice given the low dose of NDEA, the incidence of liver carcinomas increased from 0% in controls to 62% and 72% in the groups fed diets containing the low and high doses of *N*-ethylretinamide, respectively. In mice given the high dose of NDEA, the incidence of liver carcinomas increased from 15% in controls to 64% and 100%, respectively ($p < 0.01$, χ^2 test). In groups of mice fed diets containing *N*-ethylretinamide and killed at 9 or 12 months, hepatocellular carcinomas were found in 2 of 30 animals, and benign tumours were found in 6 additional mice (see section 6.2; McCormick *et al.*, 1990).

4.2.1.3 Pancreas

Hamster: Groups of 10–12 controls and 23–26 treated male and female Syrian hamsters, eight weeks of age, were given a single subcutaneous dose of *N*-nitrosobis(2-oxopropyl)amine (NBOPA) at 40 mg/kg bw. One week later, they were placed on diets containing *N*-ethylretinamide at concentrations of 0.05, 0.1 or 0.2 mmol/kg of diet. The animals were killed 33 weeks after administration of the carcinogen and examined for pancreatic cancers. The tumour incidence in animals of each sex was not significantly different from that in controls. In females, the number of pancreatic carcinomas per animal at all three doses increased from 1.2 to 2.6 ($p < 0.01$, χ^2 test). In males, the carcinoma multiplicity was 1.5 in controls and 2.3 in treated animals (not significant; Birt *et al.*, 1981).

Groups of 20–24 control and 25–40 treated male and female hamsters were given a single subcutaneous dose of 10 or 40 mg/kg bw NBOPA and one week later were placed on diets containing *N*-ethylretinamide at 0.5 or 1 mmol/kg of diet. The hamsters were killed 40 weeks after administration of the high dose of the carcinogen or 50 weeks after the low dose and examined for pancreatic cancers. The number of ductular carcinomas per animal was significantly increased in both male and female hamsters given the high dose of NBOPA and either concentration of *N*-ethylretinamide, from 0.3 to 1 for females and from 0.3 to 1.1 for males ($p < 0.05$, χ^2 test). No significant difference in tumour incidence or multiplicity was seen in animals given the low dose of NBOPA (Birt *et al.*, 1983).

4.2.1.4 Urinary bladder

Mouse: Groups of 97 control and 75 treated male $B6D2F_1$ mice were given *N*-nitrosobutyl-*N*-(4-hydroxybutyl)amine (NBHBA) at 5 or 10 mg/animal by gastric intubation twice a week for nine weeks with diets containing *N*-ethylretinamide at 0.5 or 1 mmol/kg of diet. The animals

Table 1. Effects of *N*-ethylretinamide on carcinogenesis in animals

Cancer site	Species sex, age at carcinogen treatment	No. of animals per group	Carcinogen dose, route	*N*-Ethyl-retinamide dose and route (mmol/kg diet)	Duration in relation to carcinogen	Incidence		Multiplicity		Efficacy	Reference
						Control	Treated	Control	Treated		
Trachea	Male Syrian hamsters, 20 wks	63	MNU (0.5%, intra-tracheally [total amount not stated] once a wk, 12 wks)	None 1	– 1 wk to end (6 months)	6	19*	NR	NR	Tumour enhancing	Stinson *et al.* (1981)
Liver	Female B6D2F$_1$ mice, 4–5 wks	25–29	NDEA (50 mg/kg bw, i.p.)	1 0.5	– 1 wk to end	0	72* 62*	NR	NR	Tumour enhancing	McCormick *et al.* (1990)
		27–29	NDEA (100 mg/kg bw, i.p.)	None 1 0.5	–1 wk to end	15	100* 64*	NR	NR	Tumour enhancing	
Pancreas	Female Syrian hamsters	10 23	NBOPA (40 mg/kg bw, s.c.)	0.05–0.2[a]	–1 wk to end (33 wks)	40	43	1.2	2.6*	Tumour enhancing	Birt *et al.* (1981)
	Male Syrian hamsters	12 26	NBOPA (40 mg/kg bw, s.c.)	0.005–0.2[a]	–1 wk to end (33 wks)	50	50	1.5	2.3	Ineffective	Birt *et al.* (1983)
	Female Syrian hamsters	20 (control) 37 (treated)	NBOPA (40 mg/kg bw, s.c.)	0.5–1[b]	+ 1 wk to wk 40	30	43	0.3	1.0*	Tumour enhancing	Birt *et al.* (1983)
	Male Syrian hamsters	24 (control) 40 (treated)	NBPOA (40 mg/kg bw, s.c.)	0.5–1[b]	+ 1 wk to wk 40	21	50	0.3	1.1*	Tumour enhancing	Birt *et al.* (1983)
	Female Syrian hamsters	23 (control) 25 (treated)	NBOPA (10 mg/kg bw, s.c.)	0.5–1[b]	+ 1 wk to wk 50	27	24	0.3	0.4	Ineffective	Birt *et al.* (1983)
	Male Syrian hamsters	22 (control) 30 (treated)	NBOPA (10 mg/kg bw, s.c.)	0.5–1[b]	+ 1 wk to wk 50	18	33	0.2	0.4	Ineffective	Birt *et al.* (1983)

Table 1. (contd)

Cancer site	Species sex, age at carcinogen treatment	No. of animals per group	Carcinogen dose, route	*N*-Ethyl-retinamide dose and route (mmol/kg diet)	Duration in relation to carcinogen	Incidence Control	Incidence Treated	Multiplicity Control	Multiplicity Treated	Efficacy	Reference
Bladder	Male B6D2F1 mice	(75–97)	NBHBA (5 or 10 mg/animal by gavage twice/wk for 9 wks)[c]	0.5 1.0	– 1 wk to end	37	33	NR	NR	Ineffective	Thompson *et al.* (1981)
	Male Fischer 344 rats, 6–7 wks	60 (control) 30 (treated)	NBHBA (200 mg, p.o. twice a wk. 8 wks)	2	–1 wk to 6 month	92	83	2.25	1.76	Ineffective	Thompson *et al.* (1981)
	Female Fischer 344 rats, 6–7 wks	80 (control) 40 (treated)	NBHBA (150 mg, p.o. twice a wk, 6 wks)	2	–1 wk to 6 month	35	12*	0.49	0.13*	Effective	Thompson *et al.* (1981)
	Male B6D2F$_1$ mice, 6–7 wks	99	NBHBA (7.5 mg, by gavage once a wk, 8 wks	1.5	– 1 wk to 7 month	35	21*	NR	NR	Effective	Moon *et al.* (1982)
	Female Fischer 344 rats, 50–60 g bw	200 (control) 100 (treated)	FANFT (0.2% in the diet, 10 wks)	1 2	– 1 wk to 50 wks	53	63 78*	NR	NR	Tumour enhancing	Croft *et al.* (1981)
Colon	Male Fischer 344 rats, 9 wks	40	MNU (0.5 mg, twice per wk, 8 wks, intrarectal)	2	– 5 d to 32 wks	60	65	1.71	1.65	Ineffective	Wenk *et al.* (1981)
		50	MNU (0.5 mg, twice per wk, 6 wks, intrarectal)	2	– 5 d to + 44 wks	62	63	1.55	1.58	Ineffective	Wenk *et al.* (1981)
		50	MNU (0.5 mg, twice per wk, 4 wks, intrarectal)	2	– 5 d + 52 wks	31	30	1.40	1.20	Ineffective	Wenk *et al.* (1981)

MNU, *N*-methyl-*N*-nitrosourea; i.v., intravenous; NDEA, *N*-nitrosodiethylamine; i.p., intraperitoneal; NBOPA, *N*-nitrosobis(2-oxopropyl)amine; s.c., subcutaneous; NBHBA, *N*-nitrosobutyl-*N*-(4-hydroxybutyl)amine; p.o., oral; FANFT, *N*-[4-(5-nitrofuryl)-2-thiazolyl]formamide; NR, not reported

*Significantly different from controls

[a] Data combined for three *N*-ethylretinamide doses

[b] Data combined for two *N*-ethylretinamide doses

[c] Data combined for two carcinogen doses

were killed six months after the first dose of carcinogen and examined for bladder carcinomas. Since the incidence of bladder cancer was similar at the two doses of carcinogen, the values were combined. *N*-Ethylretinamide at a dose of 0.5 mmol/kg of diet did not significantly affect the incidence of carcinomas, but at 1 mmol/kg of diet, the incidence was 21%, which was significantly lower ($p < 0.025$, χ^2 test) than that in controls (37%; Thompson *et al.*, 1981).

Groups of 99 control and 99 treated male B6D2F_1 mice were given NBHBA at 7.5 mg/animal once a week for eight weeks. One week after the final dose, the mice were placed on a diet containing *N*-ethylretinamide at 1.5 mmol/kg of diet. The animals were killed 210 days after the first dose of carcinogen and were examined for bladder carcinomas. *N*-Ethylretinamide reduced the incidence of carcinomas from 35 to 21% ($p < 0.05$, χ^2 test) (Moon *et al.*, 1982).

Rat: Groups of 60–80 control and 30–40 treated male and female Fischer 344 rats were given NBHBA by gastric intubation. Males were given 200 mg/animal twice a week for eight weeks, and females received 150 mg/animal for six weeks. One week after the final dose, the rats were placed on diets containing *N*-ethylretinamide at 2 mmol/kg diet. In females, the incidence of bladder carcinomas was 35% in controls and 12% in *N*-ethylretinamide-treated animals ($p < 0.01$, χ^2 test), and the multiplicity was reduced from 0.49 to 0.13 ($p < 0.01$, χ^2 test). In male rats, the incidence of bladder carcinomas was 92% in controls and 83% in treated animals (not significant), and the multiplicity was 2.2 in controls and 1.8 in treated animals (not significant) (Thompson *et al.*, 1981).

Groups of 200 control and 100 treated female Fischer 344 rats weighing 50–60 g were given a diet containing 0.2% *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]-formamide (FANFT) for 10 weeks and one week later were given diets containing *N*-ethylretinamide at 1 or 2 mmol/kg diet. The rats were killed 50 weeks after the first exposure to the carcinogen. The incidence of bladder carcinomas was 53% in controls, 63% at the low dose and 78% at the high dose ($p < 0.001$ [test not specified]) (Croft *et al.*, 1981).

4.2.1.5 Colon

Rat: Groups of 40–50 male Fischer 344 rats, nine weeks of age, were given MNU intrarectally at a dose of 0.5 mg per animal twice a week for four, six or eight weeks. Five days after the last dose, they were placed on diets containing *N*-ethylretinamide at 2 mmol/kg diet. The animals were killed at 52, 44 or 32 weeks after the initial dose of carcinogen. There were no appreciable differences in the incidences or multiplicity of colon carcinomas between control and treated animals (Wenk *et al.*, 1981).

4.2.2 *Intermediate biomarkers*

No data were available to the Working Group.

4.2.3 *In-vitro models*

4.2.3.1 Cellular studies

(a) Inhibition of neoplastic transformation

Neoplastically transformed foci can be produced in cultured C3H/10T/1/2 cells by application of 3-methylcholanthrene or by exposure to ionizing radiation, and various retinoids reduce the incidence of such foci. Complete inhibition of transformation was achieved when *N*-ethylretinamide was applied seven days after removal of the carcinogen and continued throughout the four-week assay. The activity was therefore not a result of changes in the metabolic activation of the carcinogen or repair of pre-carcinogenic lesions. Activity was observed at concentrations that were marginally toxic, and the inhibition was reversible upon withdrawal of the retinoids, although this was not tested with *N*-ethylretinamide. The activity of the retinoids was thus not due to cytotoxicity. A dose–response relationship was seen for reductions in focus formation with doses of 10^{-5} to 3×10^{-7} mol/L, the median effective dose being about 10^{-6} mol/L (Bertram, 1980; see Table 2). *N*-Ethylretinamide was marginally more potent than all-*trans*-retinoic acid, but the relatively low activity of all-*trans*-retinoic acid in these cells has been shown to be due to its rapid catabolism. Its activity can be increased by a factor of 1000 by simultaneous treatment with liarozole (Acevedo & Bertram, 1995), an inhibitor of an inducible cytochrome P450 4-hydroxylase enzyme which inactivates all-*trans*-retinoic acid. [The Working Group noted that it is not known if *N*-ethylretinamide is subject to similar inactivation.]

Table 2. Inhibition of cell transformation and differentiation by *N*-ethylretinamide *in vitro*

End-point	Treatment	Concentration (mol/L)	No. of foci/no. dishes	Preventive efficacy (% vehicle control)	Comments	Reference
Cell transformation	MCA 2.5 µg/ml 7 days after, then weekly	10^{-5} 3×10^{-6} 10^{-6} 3×10^{-7} Acetone Control	0/12 5/12 13/12 23.12 80/36	0 18.8 48.8 86.2 100	2–3 times more potent than all-*trans*-retinoic acid	Bertram (1980)
Differentiation	Hamster trachea; vitamin A deficiency		+	IC_{50} 1 nmol/L	30 times less potent than all-*trans*-retinoic acid	Newton *et al.* (1980)
Differentiation	Chick skin; vitamin A deficiency		+	IC_{80}, 2.2 µmol/L	Similar to all *trans*-retinoic acid	Wilkoff *et al.* (1976)

MCA, 3-methylcholanthrene; IC, inhibitory concentration

(b) Inhibition of cell differentiation.

Explants of trachea from vitamin A-deficient hamster have been used to measure the efficacy of retinoids in preventing the squamous metaplasia that usually results when this tissue is cultured in the absence of vitamin A. *N*-Ethylretinamide dissolved in dimethylsulfoxide reversed the metaplasia, at a median effective dose of about 10^{-9} mol/L when applied over 10 days. The activity of all-*trans*-retinoic acid when tested under the same conditions was 3×10^{-11} mol/L. Thus, *N*-ethylretinamide was significantly less active than the parent retinoid. More than 90% of the control cultures that had received no retinoid for the entire 10-day culture period showed metaplasia with keratin and keratohyalin granules (Newton *et al.*, 1980).

N-Ethylretinamide was also evaluated for its capacity to inhibit squamous keratinization in chick embryo metatarsal skin, which occurs in culture in the absence of adequate vitamin A. When *N*-ethylretinamide dissolved in ethanol or dimethylsulfoxide was administered for 6–8 days at a concentration of 2.2×10^{-6} mol/L, keratinization was inhibited in about 80% of exposed chick skin. all-*trans*-Retinoic acid had equivalent activity in this assay system. In the absence of exogenously added vitamin A, all the skin explants underwent squamous differentiation (Wilkoff *et al.*, 1976).

4.2.3.2 Antimutagenicity in short-term tests

No data were available to the Working Group.

4.3 Mechanisms of cancer prevention

N-Ethylretinamide inhibited transformation induced in C3H10T1/2 cells by the carcinogen, 3-methylcholanthrene (Bertram, 1980). Since the retinoid was added to the cultures seven days after removal of the carcinogen, it is not likely to have had an effect on carcinogen uptake or metabolic activation. The capacity of *N*-ethylretinamide to modulate epithelial differentiation in chick embryo skin is equivalent to that of all-*trans*-retinoic acid (Wilkoff *et al.*, 1976). This activity is evidently mediated through effects on gene activation, although *N*-ethylretinamide has no measurable affinity for the retinoid receptors (Kim *et al.*, 1994). It is not clear if *N*-ethylretinamide acts without hydrolytic cleavage to all-*trans*-retinoic acid, which occurs in a slow

enzymatic reaction catalysed by an enzyme present in liver microsomes (Shih *et al.*, 1988).

The mechanism by which *N*-ethylretinamide prevents cancer in the models of carcinogenesis in which it is effective is unknown.

5. Other Beneficial Effects

No data were available to the Working Group.

6. Carcinogenicity

6.1 Humans

No data were available to the Working Group.

6.2 Experimental models

Thirty female B6D2F$_1$ mice, 4–5 weeks of age, were fed a diet containing *N*-ethylretinamide at 1 mmol/kg of diet for 9 or 12 months. Eight animals developed hepatocellular tumours, two of which were carcinomas. No such tumours developed in control mice or in mice fed *N*-ethylretinamide at a lower dose (0.5 nmol/kg of diet; McCormick *et al.*, 1990).

N-Ethylretinamide enhanced the incidences of tracheal tumours in hamsters receiving intratracheal instillations of MNU (Stinson *et al.*, 1981), of pancreatic tumours in hamsters treated with NBOPA (Birt *et al.*, 1981, 1983), of liver tumours in mice treated with NDEA (McCormick et al., 1990) and of bladder tumours in rats given FANFT (Croft *et al.*, 1981; see section 4.2.1).

7. Other Toxic Effects

7.1 Adverse effects

7.1.1 Humans

Increased concentrations of serum lipids and increased erythrocyte sedimentation rates were seen after oral administration of a total dose of 8400 mg of *N*-ethylretinamide over three weeks to 26 patients with psoriasis. A few of the patients complained of headache, diarrhoea and vomiting (Runne *et al.*, 1973).

7.1.2 Experimental models

7.1.2.1 Acute and short-term toxicity

The toxicity of both the all-*trans* and the 13-*cis* isomers of *N*-ethylretinamide have been investigated in rats and mice after peroral and intraperitoneal administration (Sani & Meeks, 1983). The estimated LD_{50} in mice was 33 mg/kg bw for all-*trans*-retinoic acid and 1801 mg/kg bw for *N*-ethylretinamide. In 21-day studies in mice given *N*-ethylretinamide at doses of 100–1800 mg/kg bw, the haemoglobin, haematocrit, erythrocyte, leukocyte and reticulocyte counts were decreased at doses as low as 400 mg/kg bw. The anaemia-generating effect of the 13-*cis* derivative was milder than that of the all-*trans* isomer. Treatment with the *N*-ethylretinamides also increased plasma alkaline phosphatase activity and decreased serum albumin concentrations. No bone fractures were seen. Higher doses of *N*-ethylretinamide were associated with histopathological evidence of degenerative liver lesions.

7.1.2.2 Long-term toxicity

The anaemia seen after treatment with *N*-ethylretinamide was confirmed in a one-year study in rats and was related in part to retinoid-induced bone remodelling. Groups of rats given *N*-ethylretinamide at a dose of 321 or 654 mg/kg bw were compared with groups on normal diets and diets containing placebo and also with groups treated with *N*-(2-hydroxyethyl)-, *N*-butyl-, *N*-(4-hydroxyphenyl)-, *N*-tetrazol-5-yl- or 13-*cis*-*N*-ethyl-retinamides or with etretinate. The retinoids caused a narrowing of the medullary cavity and a subsequent reduction in haematopoietic capacity. The osteopathy induced by *N*-ethylretinamide was dose-dependent. At several of the doses tested, *N*-ethylretinamide and some of the other retinamides also caused significant increases in lymphoid tissue weight and peripheral blood lymphocytosis (Turton *et al.*, 1985).

7.2 Reproductive and developmental effects

7.2.1 Humans

No data were available to the Working Group.

7.2.2 Experimental models

7.2.2.1 Reproductive effects

N-Ethylretinamide induced sterility in male hamsters fed diets containing 327 mg/kg for six months. Atrophy of the terminal epithelium was observed, and the testicular weights had decreased by 75% (Stinson *et al.*, 1980).

7.2.2.2 Developmental effects

Treatment of mice with *N*-ethylretinamide at doses of 100–400 mg/kg bw on day 11 of gestation did not cause terata but mildly increased the rate of embryo resorption, indicating that the compound is minimally embryotoxic (Kochhar *et al.*, 1992). The embryo resorption rates were not increased in rats given a dose of 300 or 600 mg/kg bw, and at 600 mg/kg only 20% of the embryos were abnormal. The abnormalities were mild: only optic abnormalities were seen in the craniofacial region, and occasional incidences of dilated ureter were found in the caudal region (Turton *et al.*, 1992). In mice and rats, a dose of at least 300 mg/kg bw was required to induce teratogenic effects (Kistler, 1987). In rat whole-embryo cultures, the concentration of *N*-ethylretinamide required to produce teratogenic effects (failure of yolk sac circulation, delayed closure of the anterior neuropore, reduced number of somites) was 50–100 times that of all-*trans*-retinoic acid (Steele *et al.*, 1987).

A single oral dose of 75 mg/kg bw of all-*trans*- or 13-*cis*-retinoic acid given to pregnant hamsters increased the incidence of malformations in the offspring, but equimolar doses of *N*-ethylretinamide or 13-*cis*-*N*-ethylretinamide were not embryotoxic (Willhite & Shealy, 1984).

In an assay based on the inhibition of chondrogenesis of limb bud cells *in vitro*, *N*-ethylretinamide was active only at very high doses, 1–50 mmol/L (Kistler, 1987).

7.3 Genetic and related effects

No data were available to the Working Group.

8. Summary of Data

8.1 Chemistry, occurrence and human exposure

N-Ethylretinamide is a synthetic derivative of all-*trans*-retinoic acid. It has not been approved for use in humans.

8.2 Metabolism and kinetics

N-Ethylretinamide is slowly hydrolysed, albeit more rapidly than 4-hydroxyphenylretinamide, to all-*trans*-retinoic acid by rat liver microsomes *in vitro*. No information was available about its metabolism in humans.

8.3 Cancer-preventive effects

8.3.1 Humans

No data were available to the Working Group.

8.3.2 Experimental models

The cancer-preventive efficacy of *N*-ethylretinamide has been evaluated in models of respiratory tract and pancreas carcinogenesis in hamsters, of liver carcinogenesis in mice, of urinary bladder carcinogenesis in mice and rats and of colon carcinogenesis in rats. The tumour incidence was enhanced in the trachea and pancreas of hamsters, in the liver in mice and, in one study, in the urinary bladder in rats. *N*-Ethylretinamide had cancer-preventive effects in some studies of urinary bladder carcinogenesis in mice and rats but was ineffective in models of colon carcinogenesis.

N-Ethylretinamide inhibited carcinogen-induced neoplastic transformation at concentrations similar to those at which all-*trans*-retinoic acid had this effect. In the hamster trachea it was less potent than all-*trans*-retinoic acid in reversing squamous metaplasia; when tested in chick skin for an equivalent end-point, its activity was similar to that of all-*trans*-retinoic acid.

8.3.3 Mechanisms of cancer prevention

No relevant data were available to the Working Group.

8.4 Other beneficial effects

No data were available to the Working Group.

8.5 Carcinogenicity

8.5.1 Humans

No data were available to the Working Group.

8.5.2 Experimental models

N-Ethylretinamide was tested for carcinogenicity in one study in mice by oral administration. An increased incidence of benign and malignant liver tumours was observed. It also had tumour-enhancing effects at several sites in several species.

8.6 Other toxic effects

8.6.1 Humans

N-Ethylretinamide has been evaluated for toxic effects in human beings in only one study, which showed increased concentrations of serum lipids

after oral administration. The toxic effects seen in preclinical studies include anaemia, osteopathy and liver abnormalities.

8.6.2 Experimental models

The spectrum of effects in short-term studies of the toxicity of *N*-ethylretinamide in animals is more limited than that of other synthetic retinamide analogues, such as 4-hydroxyphenylretinamide. In a long-term study in rats, *N*-ethylretinamide induced osteopathy and haematopoietic toxicity. Like other retinoids, *N*-ethylretinamide is toxic to the male reproductive tract after long-term exposure. Its teratological effects are mild and seen only at very high doses.

9. Recommendations for Research

9.1 General recommendations for *N*-ethylretinamide and other retinoids

See section 9 of the Handbook on all-*trans*-retinoic acid.

9.2 Recommendations specific to *N*-ethylretinamide

None.

10. Evaluation

10.1 Cancer-preventive activity

10.1.1 Humans

There is *inadequate evidence* that *N*-ethylretinamide has cancer-preventive activity in humans.

10.1.2 Experimental animals

There is *evidence suggesting lack of* cancer-preventive activity of *N*-ethylretinamide in experimental animals.

10.2 Overall evaluation

There are no data on the cancer-preventive activity of *N*-ethylretinamide in humans, but there is evidence that it enhances carcinogenicity in some experimental models.

N-Ethylretinamide has not been approved for human use and is no longer produced.

11. References

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