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TOXICOLOGICAL EVALUATIONS

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TOXICOLOGICAL EVALUATION

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Imidazole

No. 203

CAS No. 288-32-4

BG Chemie
Berufsgenossenschaft der chemischen Industrie

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Imidazole

1 Summary and assessment

Imidazole is eliminated at different rates by humans and rats after single oral administration. Plasma half-life is approx. between 1.7 and 3 hours in humans, while apparently it is longer in the rat. After intravenous administration of [2-^{14}C]-imidazole to rats, 14.0 ± 2% of the radioactivity was excreted as unchanged imidazole, 38.7 ± 0.7% as hydantoin, 31.0 ± 1.2 as hydantoic acid and 4.0 ± 0.4% as additional metabolites of unknown structure within the first 24 hours. The residual activity detected in the body 24 hours after administration was predominantly located in the liver and kidneys.

Based on the available acute toxicity studies, imidazole is harmful following oral administration (LD_{50} rat oral between 220 and approx. 970 mg/kg body weight). Acute and subacute studies employing different routes of administration have reported signs of intoxication including salivation, opisthotonus, decreased food consumption, increased arterial blood pressure, vasodilatation, disturbances of balance, apathy, accelerated breathing, dyskinesia, lethargy, effects on liver enzyme activity, tonic-clonic convulsions, tremor and lateral position.

Administration to rats of imidazole at dose levels of 62.5, 125, 250 or 500 mg/kg body weight/day by oral gavage for 28 days resulted in decreased haemoglobin in females from 125 mg/kg body weight and reduced haematocrit and red blood cell counts from 250 mg/kg body weight, whereas in males these findings were observed only at the highest dose level of 500 mg/kg body weight. Additional signs noted from 250 mg/kg body weight included severe salivation (with bloody saliva from 500 mg/kg after study day 15), restlessness, hypothermia of the limbs and ruffled fur. Gross pathology revealed hepatomegaly without any histopathological correlate in most males from 125 mg/kg body weight and in most females from 500 mg/kg. Kidney effects (increased kidney weights and spotted kidney surface from 125 mg/kg body weight; increased creatinine and glutamic-pyruvic transaminase levels from 500 mg/kg body weight) occurred only in males and could be considered likely to represent species-specific lesions of the male rat which are of no relevance to humans. The *no observed*

adverse effect level (NOAEL) in this 28-day oral study in the rat was 62.5 mg/kg body weight.

In a 90-day study, imidazole was administered to Wistar rats at dose levels of 0 (control), 20, 60 or 180 mg/kg body weight/day by oral gavage. The clinical observations, ophthalmological examinations, clinical chemistry/haematology studies, organ weight determinations and gross pathological and histopathological examinations were conducted in accordance with OECD guideline No. 408. In addition, tests were carried out to assess behaviour (FOB – functional observational battery) and motor activity. Additional studies included testicular and epididymal sperm counts and sperm motility and morphology in male rats, and oestrus cycle determination in female rats. There were no treatment-related deaths or changes in body weight, body weight gain, food consumption or food efficiency compared with the control. The same applies to the ophthalmological examinations, behavioural studies (FOB), motor activity assessments and the oestrus cycle and sperm evaluations. Only the highest dose group showed treatment-related, statistically significant findings, which identified the kidney and liver as target organs. Clinical chemistry analyses revealed serum chloride and globulin decreases in both sexes. Urinalysis revealed statistically significant increases in the number of transitional epithelial cells in the urine sediments from both sexes. Relative liver weights were increased by 7.5% and 2.5% in males and females, respectively. Minimal to mild centrilobular hypertrophy was observed as a histopathological correlate in 9/10 males and 2/10 females from the highest dose group. Male rats showed an increase in kidney weight by 9.1%. Histopathology revealed all males from the highest dose group to have slight to moderate diffuse accumulation of α2u-microglobulin, as confirmed by specific antibody detection. The NOAEL is 60 mg/kg body weight/day and thus comparable with the NOAEL found in the 28-day rat study using the same route of administration.

Imidazole is severely irritating to corrosive to the skin and eye of the rabbit. In-vitro skin irritation studies have also rated imidazole as a severe irritant.

Imidazole has proved to be nonmutagenic in mutagenicity studies in Salmonella/microsome assays with and without metabolic activation. Mutagenic effects were also not observed in the UDS test in rat liver cells, in fluctuation tests with *Klebsiella pneumoniae*, *Escherichia coli* and *Citro-*

bacter freundii and in the spot test with *Bacillus subtilis*. A micronucleus assay following oral administration to mice was also negative, and therefore imidazole was devoid of genotoxicity both in vitro and in vivo.

In the N-methyl-N-nitrosourea-induced mammary cancer model in the female Sprague-Dawley rat, dietary administration of imidazole at 70 mg/kg body weight/day from study day 7 until the end of the study on day 187 failed to produce the expected protective effect. Depending on dietary fat level (3 or 20%), imidazole produced a slight tumour-enhancing effect, which was statistically significant when imidazole was administered in diet with a fat content of 20%. However, the value of the study is limited due to its failure to include a concurrent control group fed a standard diet (with a fat content of approx. 12%). In the mouse fibroblast transformation assay, imidazole produced no malignant transformations.

In a prenatal developmental toxicity study conducted in accordance with OECD guideline No. 414, imidazole (99.8%) was administered to Wistar rats at dose levels of 0 (control), 20, 60 or 180 mg/kg body weight/day by oral gavage from day 6 to 19 of gestation. Dams treated at the highest dose level, 180 mg/kg body weight, exhibited the following statistically and biologically significant findings. Transient salivation occurred in 6/25 rats for about 15 minutes shortly after dosing by gavage on days 15 to 19 of gestation. This was presumably due to a bad taste and irritation of the upper digestive tract. Food consumption was decreased during the early dosing period (days 6 to 8). Body weight gain was also reduced at this time. Evaluation of its later reduction (days 17 to 20) must also take into account the decrease in foetal weights and increase in resorptions noted at this dose level. Body weights and corrected body weights for all dose groups were similar to the control. One dam exhibited vaginal bleeding on day 20 of gestation. Significant changes observed at necropsy included decreased uterine weight and increased postimplantation loss due to late resorptions. Three out of 24 dams exhibited complete resorption at the end of the treatment period and had no live foetuses. The number of live foetuses/litter was reduced. Placental weight was increased, whereas foetal weight was decreased. Furthermore, the numbers of external malformations (anasarca and cleft palate) were increased. Visceral examination revealed one soft tissue malformation at this dose in the form of a misshapen unilateral kidney. Furthermore soft tissue variations in the form of dilated renal pelvis and ureters occurred. The numbers of skeletal malfor-

mations (shortened scapula, bent radius, bent ulna and malpositioned and bipartite sternebrae) and skeletal variations (predominantly delayed ossification) were also increased. The *no observed adverse effect level* (NOAEL) was 60 mg/kg body weight/day for both maternal toxicity and embryotoxicity/foetotoxicity. However, the observed malformations can not be explained by the maternal toxicity of imidazole. An earlier exploratory study in the rat found no indication of teratogenicity following oral administration of a single dose of imidazole at 240 mg/kg body weight on gestational day 12 or 13. An in-vitro study found malformations in rat and mouse embryos after incubation in culture medium supplemented with imidazole. However, the value of the study is greatly limited by the small number of embryos studied (6 to 10 per concentration), even more so as between 20 and 83.3% of embryos treated at the various concentrations died. A study which can only be considered exploratory found that testosterone and luteinising hormone levels in male rats were decreased following injection (no further details) of imidazole at ≥ approx. 20 mg/kg body weight, findings which led the investigators to suspect that imidazole could impair male fertility. A 90-day oral study in Wistar rats, however, found no histopathological changes in the male or female reproductive organs. The dose levels were 20 to 180 mg/kg body weight/day. Moreover, no changes were observed in the sperm parameters (testicular and epididymal sperm counts, motility and morphology) or the oestrus cycle.

A 90-day study in Wistar rats treated by gavage at dose levels up to a maximum of 180 mg/kg body weight/day found no treatment-related changes in behaviour as assessed by a functional observational battery (FOB) or in motor activity. Furthermore, histopathological examination of the brain, spinal cord and peripheral nervous system revealed no treatment-related findings. Imidazole had no degenerative effect on brain cells from rat foetuses in vitro.

Imidazole has an analgesic, anti-inflammatory, mild antipyretic and vasodilatory effect in animals. Furthermore, imidazole inhibits platelet aggregation via a mechanism involving the inhibition of thromboxane synthetases, prostaglandins, leukotrienes and thrombin. Imidazole in high-calcium medium causes increased hepatocellular mitotic activity in rat hepatocytes, while it produces the opposite effect in human epidermal keratinocyte cultures. Ex vivo, imidazole causes contraction of the smooth muscle of the

isolated guinea pig trachea and guinea pig and rabbit ileum, of the rat portal vein and of the rat and guinea pig uterus. Imidazole has an enzyme-inducing effect in rat liver microsomes in vitro and in vivo and is capable of inhibiting the development of the intestinal bacterial flora in small intestinal washings of the rat and can thus delay the inactivation of pancreatic enzymes. The enzyme-inducing effect of imidazole in the liver can result in increased degradation of sex hormones in vivo.

Imidazole had no effect on the puerperal uterus after intramuscular or intravenous administration of 100 to 250 mg to puerperal women. Amongst 29 workers employed in the production of imidazole, there were 3 cases over a period of 6.5 years of skin irritation after skin exposure to spatters of imidazole during sampling, product change over or filling procedures. Sensitisation or other imidazole-induced illnesses were not observed. According to the Informationsverbund Dermatologischer Kliniken (IVDK, Information Network of Departments of Dermatology for the surveillance and scientific evaluation of contact allergies in Germany), there have been no known cases of imidazole-related skin sensitisation at the departments of dermatology in Germany.

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area ("MAK-Kommission") has listed imidazole in the "Yellow Pages" ("Substances being Examined for the Establishment of MAK Values and BAT Values") of the List of MAK and BAT Values 2005 on the suggestion of BG Chemie in order that a MAK value be established for the chemical.

2 Name of substance

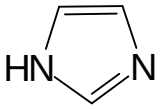
2.1	Usual name	Imidazole
2.2	IUPAC name	1H-Imidazole
2.3	CAS No.	288-32-4
2.4	EINECS No.	206-019-2

3 Synonyms, common and trade names

1,3-Diaza-2,4-cyclopentadiene
1,3-Diazole
N,N'-1,2-Ethendiylmethanimidamid
N,N'-1,2-Ethenediyl-methanimidamide
Formamidine, N,N'-vinylene
Glyoxalin
Glyoxaline
Imidazol
1H-Imidazol
Imutex
Methanimidamide, N,N'-1,2-ethenediyl-
Miazole
Pyrro(b)monazole
N,N'-Vinylenformamidin
N,N'-Vinyleneformamidine

4 Structural and molecular formulae

4.1 Structural formula



4.2 Molecular formula $C_3H_4N_2$

5 Physical and chemical properties

5.1	Molecular mass, g/mol	68.08	
5.2	Melting point, °C	88–90	(EC, 2000)
		90–91	(Falbe and Regitz, 1997)
		90.5	(Lide and Frederikse, 1997)
5.3	Boiling point, °C	ca. 136 (at 13 hPa)	(EC, 2000)
		256	(Ebel et al., 2002)
		257	(Lide and Frederikse, 1997)
		268	(EC, 2000)
5.4	Vapour pressure, hPa	0.003 (at 20 °C)	(EC, 2000)

5.5	Density, g/cm³	1.0303 (at 101 °C) (Lide and Frederikse, 1997) 1.0257 (at 110 °C) (Ebel et al., 2002)
5.6	Solubility in water	633 g/l (at 20 °C) (EC, 2000) 241 g/100 ml (at 20 °C) (Ebel et al., 2002)
5.7	Solubility in organic solvents	Readily soluble in chloroform, ether and pyridine; slightly soluble in benzene (Falbe and Regitz, 1997)
5.8	Solubility in fat	Partition coefficient log P_{ow}: −1.319 (calculated) (EC, 2000) Partition coefficient log P_{ow}: −0.02 (measured) (EC, 2000)
5.9	pH value	10.5 (at 67 g/l H_2O, 20 °C) (EC, 2000)
5.10	Conversion factor	1 ml/m³ (ppm) ≙ 2.83 mg/m³ 1 mg/m³ ≙ 0.35 ml/m³ (ppm) (at 1013 hPa and 25 °C)

6 Uses

Intermediate in the manufacture of plant protection agents, photographic chemicals, dyes, ion exchangers, pharmaceuticals, 1-vinylimidazole and cyanoethylimidazole, and as a catalyst or hardener e.g. for polyurethane foams and epoxy resins and a nucleophilic catalyst for silylations and acylations (BASF, 1996; Ebel et al., 2002, Falbe and Regitz, 1997).

7 Experimental results

7.1 Toxicokinetics and metabolism

Following single oral administration of imidazole to Wistar rats (aged 2 months, n = 4 or 5) at 0.24 mmol/kg body weight (equivalent to 16.3 mg/kg body weight), plasma imidazole levels were 8.9 µg/ml after 6 and 12 hours, 6.1 µg/ml after 24 hours and 2.0 µg/ml after 48 hours. Imidazole was no longer detectable in plasma at 96 hours after administration. The limit of detection was 0.02 mmol/l (equivalent to 1.36 µg/ml; Pagella et al., 1983).

Male Wistar rats (180 to 200 g) treated with a single intravenous dose of 3 µmol (150 µCi) [2-^{14}C]-imidazole excreted 14.0 ± 2% of the radioactivity as unchanged imidazole, 38.7 ± 0.7% as hydantoin, 31.0 ± 1.2% as hydantoic acid and 4.0 ± 0.4% as additional, structurally unidentified metabolites in the urine within the first 24 hours after administration. Pretreatment with the cytochrome P450 inhibitor SKF525-A increased the excretion of unmetabolised imidazole while at the same time reducing hydantoin and hydantoic acid, whereas pretreatment with the cytochrome P450 inducers 3-methylcholanthrene and phenobarbitone had no significant effect on urinary metabolites. The residual radioactivity at 24 hours after administration, given as nmol equivalents based on the amount of imidazole/g tissue or per ml body fluid, was located primarily in the liver (approx. 0.35 nmol/g), kidneys (approx. 0.12 nmol/g) and aorta (approx. 0.1 nmol/g). The levels of radioactivity found in plasma, blood, heart, lung, brain, muscle, skin and cartilage were all below approx. 0.03 nmol per g or ml. The fatty tissue contained no detectable radioactivity. More detailed studies of the radioactivity retained in the aortic tissue revealed that it was essentially bound to elastin and that binding was enhanced by pretreatment with SKF525-A but was not affected by 3-methylcholanthrene or phenobarbitone. In in-vitro studies, the radioactivity bound to the elastin in the aortic tissue was dependent on cupro-ascorbate-catalysed reactions (Ohta et al., 1996, 1998).

Imidazole 2-hydroxybenzoate is a salt consisting of 1 mol each of imidazole and 2-hydroxybenzoeic acid (salicylic acid). It possesses a broad spectrum of anti-inflammatory activity. Imidazole, one of the two components, has been demonstrated to act as a free radical scavenger in bovine synovial fluid (Puig-Parellada and Planas, 1978). A study by Pagella et al. (1984) therefore undertook to investigate the penetration of the two components of the salt – imidazole and salicylate – into pleural exudates after oral administration to male Sprague-Dawley rats (1 mmol/kg body weight) and into knee joint exudates after intravenous administration to male New Zealand rabbits (0.5 mmol/kg body weight). Pleurisy was induced by intrapleural injection of carrageenin, while inflammation of the knee joint was produced by a urate-cotton pellet implantation into the knee joint. Serum and pleural exudates were collected from rats at 2, 4, 8, 16 and 24 hours after oral administration and the samples analysed for imidazole and salicylate levels. Both components penetrated rapidly into the inflamed sites, although imidazole, which diffused without any specific localisation, i.e. into

inflamed and non-inflamed fluids, showed a different kinetic behaviour from salicylate, which preferentially accumulated in the inflammatory fluids, where it remained longer than imidazole. Maximum concentrations of imidazole in serum and exudates, 0.43 and 0.45 mmol/l (pleura) and 0.34 mmol/l (knee joint), were attained after 2 hours. The half-life was 4 hours. Imidazole was no longer detectable in serum or exudates after 16 hours (Pagella et al., 1984).

The administration of 750 mg imidazole 2-hydroxybenzoate as a tablet or suppository produced respective peak imidazole plasma concentrations of 3.4 ± 0.26 and 2.78 ± 0.25 µg/ml in 10 healthy subjects (4 men, 6 women). Maximum plasma concentrations were observed after 86.3 ± 10.9 minutes (tablet) and 75.2 ± 5.4 minutes (suppository). The half-lives of elimination from plasma were 1.70 ± 0.19 hours (tablet) and 1.78 ± 0.26 hours (suppository). Plasma samples were collected before administration and at 30, 60, 90, 120, 240, 360 and 480 minutes after administration (Noseda et al., 1988).

The pharmacokinetic profile, protein binding, relative bioavailability and metabolism of imidazole as the main component of the nonsteroidal anti-inflammatory agent imidazole 2-hydroxybenzoate was studied in male subjects after single and multiple oral administration of tablets or drops. Groups of 18 healthy male subjects (aged 18 to 25 years) of ideal body weight (within 20%), underwent comprehensive medical, biochemical and haematological examination before and after substance administration. They were given one 750 mg tablet (containing 750 mg imidazole 2-hydroxybenzoate) or a single dose of 40 drops (containing a total of 400 mg imidazole 2-hydroxybenzoate). In the multiple-dose study, the subjects received three times one tablet or three times 40 drops/day for another 2 days starting 48 hours after the initial dose. On study day 4, only the morning dose was administered. Very large numbers of blood and urine samples were collected and comprehensive laboratory tests were performed. The maximum concentration (C_{max}) of imidazole observed after single and multiple administration of the two dosage forms (tablets and drops), the times to maximum concentration (T_{max}), and the plasma half-lives are summarised in Table 1.

Table 1. Summary of the pharmacokinetic parameters (plasma levels and standard deviations) of imidazole following single or multiple administrations of imidazole 2-hydroxybenzoate as tablets or drops

	Single administration		Multiple administration	
	Tablets	Drops	Tablets	Drops
C_{max} [1]	3.59 ± 0.96	3.3 ± 1.22	A 2.87 ± 0.84	A 2.67 ± 1.22
			B 3.11 ± 0.78	B 2.30 ± 0.61
T_{max} [2]	0.79 ± 0.54	0.71 ± 0.59	A 1.04 ± 0.50	A 0.96 ± 0.67
			B 0.68 ± 0.51	B 0.51 ± 0.52
$T_{½}$ [3]	2.98 ± 1.13	2.48 ± 1.19	A 2.85 ± 1.25	A 3.47 ± 2.64
			B 1.86 ± 0.78	B 2.12 ± 0.91

[1] µg imidazole/ml plasma
[2] time to C_{max}, in hours
[3] plasma half-life, in hours
A first dose
B 10th (last) dose

The parameters presented in Table 1 clearly show that peak plasma concentrations were rapidly attained following single or multiple administration of tablets or drops, thus indicating fast absorption. Plasma levels dropped very rapidly after attainment of the peak plasma concentration. The plasma half-lives of the two dosage forms were similar and no signs of accumulation were observed. Imidazole 2-hydroxybenzoate, the originally administered organic salt of imidazole and salicylic acid, was not found in the monodrug form in either plasma or urine, where it was present only as imidazole and salicylic acid. Renal elimination of imidazole was approx. 10 to 15% of the dose, which led the investigators to conclude that the major route of excretion was extrarenal (e.g. via the enterohepatic circulation). The protein binding of imidazole was 5 to 15%. The metabolites hydantoin and hydantoic acid were below the level of detection as no radioactive label was used. The decrease in plasma half-life seen after multiple administrations led the investigators to assume that imidazole had an enzyme-inducing effect. The relative bioavailabilities of imidazole after single and multiple administrations were calculated as 138% and 113%, respectively (Kuemmerle et al., 1986).

7.2 Acute and subacute toxicity

The following LD_{50} values were determined following single-dose administration of imidazole:

Rat	oral	between 220 and approx. 970 mg/kg body weight
Mouse	oral	between 880 and 1880 mg/kg body weight
Guinea pig	oral	760 mg/kg body weight
Rat	intraperitoneal	620 mg/kg body weight
Mouse	intraperitoneal	between 300 and 620 mg/kg body weight
Mouse	intravenous	475 (male) or 507 (female) mg/kg body weight
Rat	subcutaneous	627 mg/kg body weight
Mouse	subcutaneous	between 560 and 817 mg/kg body weight

Therefore the chemical is to be considered harmful (see also Table 2).

Beginning of Table 2

Table 2. Acute toxicity of imidazole

Species/ strain	No. of animals/ dose	Sex	Route of administration	Observation period (days)	LD_{50} (in mg/kg body weight; 95% confidence range)	Reference
Rat	n.d.	n.d.	oral	n.d.	ca. 970	BASF, 1956
Rat	n.d.	n.d.	oral	n.d.	220	Anonymous, 1993
Mouse	n.d.	n.d.	oral	n.d.	880	Italfarmaco, 1983
Mouse (Swiss)	n.d.	female	oral	7	1191 (1070–1327)	Pagella et al., 1983
Mouse (Swiss)	n.d.	male	oral	7	1321 (1183–1476)	Pagella et al., 1983
Mouse	10	male	oral	n.d.	1880 ± 45	Nishie et al., 1969
Guinea pig	n.d.	n.d.	oral	n.d.	760	Anonymous, 1993
Unspecified	n.d.	n.d.	oral	n.d.	1000–1500	Anonymous, 1966
Rat (Wistar)	n.d.	male	intraperitoneal	3	620 (496–775)	Ferrari, 1985
Mouse	10	male	intraperitoneal	7	300–500	Doull et al., 1962

Table 2. Acute toxicity of imidazole						
Species/ strain	No. of animals/ dose	Sex	Route of administration	Observa-tion period (days)	LD_{50} (in mg/kg body weight; 95% confidence range)	Reference
Mouse	n.d.	n.d.	intraperitoneal	n.d.	ca. 520	BASF, 1956
Mouse	10	male	intraperitoneal	n.d.	610 ± 7.4	Nishie et al., 1969
Mouse (Swiss)	n.d.	male	intraperitoneal	3	580 (464–725)	Ferrari, 1985
Mouse (Swiss)	n.d.	male	intravenous	7	475 (457–493)	Pagella et al., 1983
Mouse (Swiss)	n.d.	female	intravenous	7	507 (472–544)	Pagella et al., 1983
Rat (Wistar)	n.d.	n.d.	subcutaneous	n.d.	627 (586–681)	Angelakos and Loew, 1957
Mouse	n.d.	n.d.	subcutaneous	n.d.	ca. 560	BASF, 1956
Mouse (Swiss)	n.d.	n.d.	subcutaneous	n.d.	817 (681–953)	Angelakos and Loew, 1957
Dog	n.d.	n.d.	subcutaneous	n.d.	28	Anonymous, 1993
n.d. no data						

End of Table 2

Signs of toxicity observed in the rat and mouse after oral, intraperitoneal, intravenous or subcutaneous administration included salivation, opisthotonus, decreased food consumption, disturbances of balance, dyskinesia, lethargy, apathy, dyspnoea, tonic-clonic convulsions, tremor and lateral position (BASF, 1956; Bergner et al., 1969; Ferrari, 1985; Ferrari and Baggio, 1985 a, b; Ferrari et al., 1986; Nishie et al., 1969; Pagella et al., 1983; Roussinov et al., 1976).

Subcutaneous administration was additionally associated with necrotic foci at the injection site (BASF, 1956).

A rabbit (weighing 1670 g) given imidazole in 3 subcutaneous doses of 250 mg (equivalent to approx. 150 mg/kg body weight) within 40 minutes was easily startled for a short period one hour after the first dose, or 10 minutes after the last dose, and showed signs of weakness following the second and third doses but then behaved completely normally again. The urine collected during the following 24 hours was detected to contain abundant quantities of imidazole (no further details; Auvermann, 1918).

A cat (weighing 1900 g) given a single subcutaneous dose of imidazole of 250 mg (equivalent to 132 mg/kg body weight) showed retching, licking movements, accelerated breathing, salivation, vomiting, tremor, reduced

body temperature and weakness, and weight loss to 1500 g occurred within a few days. The animal died after 7 days. Another cat (weighing 1500 g) given a single subcutaneous dose of imidazole of 250 mg (equivalent to 167 mg/kg body weight) exhibited mild mydriasis, irregular breathing, dyspnoea, vomiting and a decrease in body temperature. The animal was free of clinical signs the next day (no further details; Auvermann, 1918).

Sprague-Dawley rats received aqueous solutions containing imidazole at 62.5, 125, 250 or 500 mg/kg body weight/day 5 times per week for 28 days by oral gavage. The purity was 99%. Groups of 10 animals per sex and concentration were used for exposure and additional groups of 10 animals per sex served as controls. Study parameters included behaviour and clinical signs of toxicity, mortality, food consumption and body weight gain, haematology (haemoglobin, haematocrit, MCV (mean corpuscular volume), MCHC (mean corpuscular haemoglobin concentration), red cell, white cell and differential counts) and biochemistry (Na^+, K^+, Ca^{++}, Cl^-, CO_2, phosphate, glucose, urea, total protein, total lipids, total bilirubin, creatinine, glutamic-pyruvic transaminase, alkaline phosphatase) and urine tests (pH, protein, glucose, urobilinogen, sediment). At the end of the study, gross and histopathological examinations were performed on the brain, pituitary gland, heart, lungs, thyroid gland, liver, kidneys, adrenal glands, spleen, stomach, small intestines, large intestines, pancreas, mesenteric lymph nodes, urinary bladder, testes and ovaries. From 250 mg/kg body weight, imidazole caused mild to severe salivation (from study day 16), and 500 mg/kg body weight caused restlessness, hypothermia of the limbs, ruffled fur and severe salivation with bloody saliva in occasional animals from study day 15. Food consumption and body weight gains in males were in the range of the control group. At the high dose level, body weight gain was approx. 5% lower than the control values throughout the study. From 125 mg/kg body weight, females showed significant increases in food consumption and body weight gain in study weeks 2 and 4. No deaths occurred. After 4 study weeks, females had decreases in haemoglobin from 125 mg/kg body weight and decreases in haematocrit and red blood cell counts from 250 mg/kg that were significantly below the normal variability range, whereas only the high-dose males had significant, substance-related decreases in haemoglobin and haematocrit values. Creatinine and glutamic-pyruvic transaminase levels in high-dose males were significantly higher than the control values. Gross pathology revealed hepatomegaly in

5 to 10 animals per sex and dose level in males from 125 mg/kg body weight and high-dose females given 500 mg/kg body weight as well as a spotted kidney surface in males from 125 mg/kg body weight. These findings were reflected in the significant increases observed in relative liver weights for males and females from 125 mg/kg body weight and in kidney weights (males from 250 mg/kg body weight) as well as in the significant increases in absolute liver and kidney weights seen in females from 125 mg/kg body weight. In addition, absolute heart weight was significantly increased in females from 125 mg/kg body weight whereas relative heart weight was significantly increased only in the highest dose group given 500 mg/kg body weight. Absolute adrenal weights were statistically significantly increased only in the 125 mg/kg and the 500 mg/kg groups of males and females, respectively. However, histopathological examination revealed no remarkable findings (BASF, 1976). The *no observed adverse effect level* in this study was 62.5 mg/kg body weight/day.

7.3 Skin and mucous membrane effects

A skin irritation study of crude imidazole (approx. 95% pure) and technical-grade imidazole (approx. 100% pure) conducted in white rabbits involved exposure of the dorsal skin for periods of 5, 15 or 60 minutes. The two imidazole samples were administered in the form of an approx. 80% aqueous paste made with distilled water and as a 50% aqueous solution (pH approx. 7 and 10), respectively. Following exposure, the treated skin area was washed first with undiluted polyethylene glycol 400 and subsequently with a 50% aqueous solution of polyethylene glycol 400. No primary skin irritation occurred after exposure for 5 minutes. Exposure for 15 or 60 minutes to the aqueous paste resulted in inflammatory red patches with mild swelling and subsequent formation of brown pigmented scales or scabs and bleeding, which showed partial healing with scarring. Exposure to the 50% aqueous solutions adjusted to pH 7 or 10 for 15 or 60 minutes resulted in transient, barely perceptible reddening, which cleared up within a few hours. No fundamental difference between crude imidazole and technical-grade imidazole was noted in these studies (BASF, 1956).

In a patch test, the clipped dorsal skin of rabbits (White Vienna) was exposed to a patch (2 cm x 2 cm) loaded with 0.5 ml of an 80% aqueous

formulation of imidazole for 1 or 4 hours (“corrosion test”). Upon removal of the patch, the treated skin area was washed polyethylene glycol 400 and subsequently with a mixture of polyethylene glycol 400 and water (1 : 1). After 1-hour exposure, the 4 rabbits (one male and 3 females) in the study showed mild reddening of the skin. Mild reddening and mild oedema were observed on the following two days of the study. The oedema resolved completely by day 8 of the post-exposure observation period. Residual signs included patchy, superficial necrotic lesions in addition to scaling. Immediately after 4-hour exposure, the 2 exposed rabbits exhibited severe reddening of the area of exposure and beyond, accompanied by severe oedema. Soft necrosis and marked oedema were observed 24 hours after application. Mild oedema and necrosis with a parchment-like or leathery appearance were still visible at the end of the 8-day post-exposure observation period. No signs of absorptive intoxication were observed after 1 and 4 hours of exposure. Imidazole was considered corrosive based on the results obtained after 4-hour exposure (BASF, 1979 a).

In another patch test the intact or scarified dorsal skin of 3 white rabbits was exposed for 24 hours to a patch (ca. 2.5 cm x 2.5 cm) soaked with approx. 0.5 ml of an aqueous formulation containing 80% imidazole. At 24 hours after application, the intact and scarified skin showed soft necrosis and marked oedema. During the 8-day post-exposure observation, the necrotic lesions developed a parchment-like appearance, while oedema severity remained almost unchanged. No signs of absorptive intoxication were observed. Based on the readings at 24 and 72 hours after study initiation the primary irritation index was calculated as approx. 5.6 out of a maximum of 8.0 (BASF, 1979 b). Based on these results, imidazole has to be judged as severely irritating to corrosive to the skin.

An eye irritation study was conducted with crude imidazole (approx. 95% pure) and technical-grade imidazole (approx. 100% pure). To this end, approx. 0.1 g of either imidazole product was introduced into the conjunctival sac of the rabbit eye in the crystalline form or as one drop of a 50% aqueous imidazole solution (pH approx. 7 or 10) and then gently spread over the surface of the eye. Crystalline imidazole caused severe reddening and swelling of the conjunctivae in addition to marked diffuse corneal opacity. The acute inflammatory signs resolved within 10 to 12 days without causing lasting damage. The irritation caused by the 50% aqueous solution adjusted to approx. pH 10 practically resembled that caused by the powdered

substance, while the 50% aqueous solution adjusted to approx. pH 7 produced markedly less irritation (mild redness and oedema). There was no difference between crude imidazole and technical-grade imidazole. Imidazole was severely irritating to the eye in this study (BASF, 1956).

In a further eye irritation study, 3 rabbits (White Vienna, 2 males, 1 female) had approx. 0.1 ml (bulk volume) imidazole instilled into the conjunctival sac of the right eye. Marked corneal opacity and mild inflammation of the iris were evident 24 hours after instillation into the eye. The conjunctivae were markedly reddened and there was readily visible conjunctival oedema with increased lacrimation. Observed manifestations of irreversible tissue damage included grey discoloration of the nictitating membrane after 24 hours and white discoloration of the nictitating membrane, eyelid scarring and alopecia around the eyelid after 8 days. The signs did not resolve after 8 days. Based on the readings at 24, 48 and 72 hours after study initiation, the average irritation index on the Draize scale was 57.4 out of a maximum score of 110 (BASF, 1979 c). Thus, imidazole was severely irritating to corrosive to the eye.

Imidazole was studied in vivo in 3 rabbits for mucous membrane irritation as a reference substance for the validation of alternative in-vitro methods for mucous membrane irritation testing. The study was carried out in accordance with Directives 84/449/EEC and 91/325/EEC and the French 1984 and 1991 guidelines for testing. Each animal had 100 mg of the 99% pure crystalline substance instilled into the conjunctival sac of one eye. The eyes were rinsed with 0.9% NaCl solution one hour after instillation. Assessments were performed after one hour and after 1, 2, 3, 4, 7 and 14 days. Corneal lesions were made visible using fluorescein solution. Treatment resulted in corneal opacity to the degree of transient complete opacity, marked inflammatory reactions of the iris and conjunctival changes with very severe diffuse reddening and marked to very severe swelling and marked ocular discharge. The findings were not reversible by 7 days after administration and only partially reversible by 14 days after administration. No examination was performed after 21 days. A mean irritation index after 3 days, the time when irritation was observed to be greatest, was calculated as 59.3 out of a maximum irritation score of 110, and imidazole was evaluated as severely irritating. The mean irritation indexes after one day and 14 days were calculated as 48 and 43, respectively (Balls et al., 1995;

ECETOC, 1998; Gautheron et al., 1994 a, b; Gilleron et al., 1996). Note: Gautheron et al. (1994 b) give the mean irritation index after 3 days as 54.3.

The in-vitro mucous membrane irritation studies of imidazole are summarised in Table 3 below. As in the in-vivo studies, imidazole was evaluated as severely irritating in the majority of the trials (see Table 3).

Table 3. Activity of imidazole in in-vitro test systems for assessing mucous membrane effects

Test system	Parameters studied, result	Evaluation	Reference
Bovine Corneal Opacity and Permeability (BCOP) Assay; interlaboratory study with 12 participating laboratories, 10-minute incubation of bovine corneas with a 20% formulation of the test substance	Measurement of corneal opacity and permeability to fluorescein; mean irritation index for the 12 institutes was 87.9 with a range from 62 to 140; evaluation as severely irritating if the index was ≥ 55.1	severely irritating	Gautheron et al., 1994 b
Bovine Corneal Opacity and Permeability (BCOP) Assay; 4-hour incubation of bovine corneas with a 20% formulation of the test substance	Measurement of corneal opacity and permeability to fluorescein; mean irritation indices in two independent test series were 120.7 and 111.3; evaluation as severely irritating if the index was ≥ 55.1	severely irritating	Harbell and Curren, 1998
Mouse cornea permeability test; one-minute exposure of the mouse cornea to undiluted test substance	Determination of corneal permeability to the fluorescent dye sulforhodamine B; irritation index 10 out of a maximum score of 10	irritation index of 10 (maximum irritation index)	Maurice and Brooks, 1995
Madin-Darby canine kidney (MDCK) cells permeability assay; 15-minute incubation of canine kidney cell monolayers with different test concentrations	Determination of the concentrations of test substance resulting in 20% and 50% permeability of the canine kidney cell monolayer to fluorescein (fluorescein leakage); a concentration of 52.0 mg/ml resulted in 50% permeability (FL50 value of 52); evaluation as severely irritating if FL50 values were ≤ 100	severely irritating	Gautheron et al., 1994 a
Hen's egg test–Chorioallantoic membrane (HET-CAM-TSA) assay; 20-second exposure to crystalline test substance applied to the area defined by a Teflon ring placed onto the chorioallantoic membrane of a 10-day incubated hen's egg; two independent studies	standardised time-dependent microscopic assessment of the chorioallantoic membrane after contact with the test substance compared with untreated areas of the membrane; respective irritation indices calculated as 187 ± 0.9 and 19.43 ± 0.49; evaluation as irritating (no distinction between moderate, severe or extreme) for indices from 5.0 to 21.0	irritating	Gilleron et al., 1996, 1997
Neutral Red Uptake Assay; interlaboratory study with 4 participating laboratories; 24-hour incubation of BALB/c 3T3 clone A31 mouse cells with formulations containing test substance concentrations of up to 1%	Measurement of neutral red uptake by cell monolayer cultures and determination of an NR_{50} value (concentration causing in a 50% reduction in neutral red uptake relative to the control) followed by extrapolation to a Draize index in the range from 0 to 110; mean extrapolated Draize index for the 4 laboratories was 15.83, range 12.94 to 18.43	irritation index of 15.83 out of a maximum of 110	Brantom et al., 1997; Jones et al., 1999

7.4 Sensitisation

No information available.

7.5 Subchronic and chronic toxicity

In a gavage study, Wistar rats were administered imidazole (99.8% pure) at dose levels of 0 (vehicle control, water), 20, 60 or 180 mg/kg body weight/day for 90 days. The clinical observations, ophthalmological examinations, clinical chemistry/haematology studies, organ weight determinations and gross pathological and histopathological examinations were conducted in accordance with OECD guideline No. 408. In addition, tests were carried out to assess behaviour (FOB – functional observational battery) and motor activity. Studies included testicular and epididymal sperm counts and sperm motility and morphology in male rats, and oestrus cycle determination in female rats. There were no treatment-related deaths, and body weight, body weight gain, food consumption and food efficiency were also unaffected. The same applies to the results of the ophthalmological examinations, behavioural studies (FOB) and motor activity assessments as well as the oestrus cycle and sperm results. Only after administration of 180 mg/kg body weight/day were treatment-related findings observed, which identified the kidney and liver as target organs. At this level, the clinical chemistry studies revealed statistically significant chloride and serum globulin decreases in both sexes. Females additionally exhibited decreased total protein and albumin levels. Urinalysis revealed statistically significant increases in the number of transitional epithelial cells in the urine sediments from both sexes. There were no other abnormal clinical chemistry/haematology findings. Relative liver weights were statistically significantly increased by 7.5% and 2.5% in males and females, respectively. Minimal to mild centrilobular hypertrophy was observed as a histopathological correlate in 9/10 males and 2/10 females from the highest dose group. Male rats showed a statistically significant increase in kidney weight by 9.1%. Histopathology revealed all males to have slight to moderate diffuse accumulation of α2u-microglobulin in the epithelia and lumina of the proximal tubules of the renal cortex. This was demonstrated by both Mallory-Heidenhain staining (nonspecific) and a specific antibody detection method. In summary, it can be concluded that the administration of imida-

zole to rats by gavage for 90 days caused treatment-related findings only at the highest dose level, the lesions identifying the liver and kidneys as the target organs. The NOAEL was 60 mg/kg body weight/day and is thus comparable with the NOAEL found in the 28-day rat study using the same route of administration (BASF, 2002 a).

7.6 Genotoxicity

7.6.1 In vitro

Imidazole (99.9% pure) was tested for mutagenicity in the standard plate test and the preincubation test with and without metabolic activation with Aroclor 1254-induced liver S-9 mix using the *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 (in accordance with OECD guideline No. 471). No bacteriotoxicity or mutagenicity was observed in the studied concentration range, from 20 to 5000 µg/plate (BASF, 1992).

Imidazole was studied for mutagenicity in the direct plate test using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535,TA 1537 and TA 1538 as well as *Escherichia coli* WP/2Hcr$^-$. The concentrations of imidazole ranged from 10 up to 2000 µg/plate. No bacteriotoxic effect was observed. The study was carried out only in the absence of metabolic activation. There was no indication of mutagenicity (Momii et al., 1979).

Preincubation plate tests using *Salmonella typhimurium* strains TA 1535 or TA 1537 showed imidazole (99% pure) to be nonmutagenic at concentrations of 34.1 or 68.1 µg/plate in the absence or presence of metabolic activation (S-9 mix from sodium phenobarbitone and β-naphthoflavone-induced rat liver). No bacteriotoxic effect was observed (Gatehouse and Wedd, 1983).

When a Salmonella/microsome assay was carried out using *Salmonella typhimurium* strains TA 97, TA 98, TA 100 and TA 102, imidazole (> 99% pure) showed no mutagenic potential in the presence or absence of metabolic activation with S-9 mix from β-naphthoflavone and phenobarbitone or Aroclor 1254-induced rat liver). Bacteriotoxicity was also not observed in the studied concentration range from 0.625 to 10.0 mg/plate. Moreover, hydantoin and N-acetyl-imidazole, the metabolites of imidazole that were also investigated, were equally devoid of mutagenic activity (Forster et al., 1992).

Imidazole was found as a Maillard reaction product (nonenzymatic browning) in various cooked meats in Japan. In addition, the three so-termed IQ-type mutagens IQ (2-amino-3-methylimidazo[4,5-f]quinoline), MeIQx (2-amino-3,4-dimethylimidazo[4,5-f]quinoxaline) and MeIQ (2-amino-3,4-dimethylimidazo[4,5-f]quinoline) were detected in boiled pork juice. In order to investigate whether Maillard reaction products were involved in the formation of the IQ-type mutagens, the boiled pork juice was tested for genotoxicity after preparation, using the plate incorporation assay with *Salmonella* typhimurium strain TA 98 with and without added imidazole in the presence of Aroclor 1254-induced rat liver S-9 mix. Whereas the meat juice proved mutagenic (704 ± 109 revertants/plate), the addition of imidazole (126 µM) failed to significantly reduce the number of revertants/plate (142 ± 34 revertants/plate; no indication whether a concurrent control was included; Lee et al., 1995).

A UDS test of imidazole (> 99% pure) was performed in three independent experiments in primary rat liver cells exposed to concentrations (0.25 to 4.00 mg/ml) which extended into the toxic range (highest concentration). Imidazole did not induce an increased rate of DNA repair (Forster et al., 1992).

The fluctuation test with *Klebsiella pneumoniae*, *Escherichia coli* K12 · Hfr Hayes and *Citrobacter freundii* also gave no indication of mutagenic properties. Streptomycin resistance served as an indicator. Imidazole was tested at a concentration level of 20 mmol/l (equivalent to 1.36 mg/ml) in *Klebsiella pneumoniae* (no further details; Voogd, 1975; Voogd et al., 1979).

The spot test with *Bacillus subtilis* H 17 (Rec^+) and M 45 (Rec^-) also gave no indication of mutagenic properties of imidazole at concentrations from 10 to 1000 µg/filter paper disc (Momii et al., 1979).

7.6.2 In vivo

A micronucleus test in accordance with OECD guideline No. 474 was conducted in groups of 5 male and 5 female NMRI mice which were dosed once by oral gavage with imidazole (as imidazole hydrochloride, 99.5% pure) at dose levels of 500, 1000 or 2000 mg/kg body weight. At 24 hours,

and in the high dose group at 16, 24 or 48 hours, 1000 polychromatic erythrocytes per animal were prepared from the bone marrow of the femora and analysed for the presence of micronuclei. The results were compared with those obtained for a negative control and two positive control groups (cyclophosphamide, vincristine). The number of micronucleated polychromatic erythrocytes was not increased in any of the dose or preparation groups. Moreover, no change was detected with respect to the ratio of polychromatic to normochromatic erythrocytes and hence no inhibition of erythropoiesis was observed. Thus imidazole showed no chromosome-damaging or spindle poison effects in this study (BASF, 1993).

7.7 Carcinogenicity

The anticarcinogenic or chemopreventive action of imidazole (> 99% pure) as an inhibitor of thromboxane synthetase was studied in chemically induced mammary carcinogenesis in the rat. Female Sprague-Dawley rats were given a single subcutaneous injection of N-methyl-N-nitrosourea at 40 mg/kg body weight and then fed imidazole (1000 mg/kg diet, equivalent to approx. 70 mg/kg body weight/day) in their diet from 7 days after the injection until the end of the study (study duration: 187 days). Imidazole had no preventive effect on the formation of mammary tumours, a finding which led the investigators to conclude that the chemical inhibition of thromboxane synthetase did not present a useful mechanism for the chemoprevention of mammary cancer. By contrast, depending on dietary fat level (3 or 20%), administration of imidazole resulted in an increase in the incidence of mammary cancers from 78 to 92% with the low-fat diet and a significant increase to 96% with the high-fat diet. The data analysis encompassed only such tumours that were histologically confirmed malignant mammary cancers but not the benign mammary tumours (< 0.2 tumours/rat in all groups), which were infrequently observed in this study. Moreover, tumour latency was decreased in the groups treated with imidazole while the number of tumours/rat was increased (by 30% in the low-fat diet group; not statistically significant; see Table 4). Body weight was statistically significantly depressed by imidazole administration in both diet groups. Tumour-related mortality was unaffected, and no organ-specific toxicity attributable to imidazole was evident at necropsy.

Table 4. Influence of imidazole on MNU-induced mammary carcinogenesis

Group	Number of animals used	MNU dose (mg/kg body weight)	Dietary fat level (%)	Imidazole dose (mg/kg diet[3])	Cancer incidence (%)	Tumour latency (T_{50}, days)	Carcino-mas/rat	Body weight (g)
1	20	0	3	0	0		0	298 ± 10
2	10	0	3	1000	0		0	295 ± 6
3	20	0	20	0	0		0	297 ± 10
4	10	40	20	1000	0		0	280 ± 7
5	50	40	3	0	78	120	2.16	292 ± 5
6	25	40	3	1000	92	99	2.77	277 ± 5[1]
7	50	40	20	0	78	98	2.67	287 ± 5
8	25	40	20	1000	96[1]	75	2.69	269 ± 4[2]

MNU N-Methyl-N-nitrosourea
[1] $p < 0.05$ versus appropriate control group
[2] $p < 0.01$ versus appropriate control group
[3] equivalent to approx. 70 mg/kg body weight/day

Thus imidazole had a slight tumour-enhancing effect in this N-Methyl-N-nitrosourea-induced mammary cancer model in the female Sprague-Dawley rat, the effect being statistically significant when imidazole was administered in diet with a fat content of 20% (McCormick et al., 1989). The value of the study is limited due to its failure to include a concurrent control group fed a standard diet (with a fat content of approx. 12%).

In the M2-C3H mouse fibroblast transformation assay, imidazole (> 99% pure) produced no malignant transformations in the concentration range from 100 to 4000 µg/ml (Forster et al., 1992).

7.8 Reproductive toxicity

In a prenatal developmental toxicity study conducted in accordance with OECD guideline No. 414, imidazole (99.8%) was administered by oral gavage to Wistar rats from day 6 to 19 of gestation. The dose levels were 0 (vehicle control, water), 20, 60 or 180 mg/kg body weight/day. During the study, the dams were assessed for clinical observations, body weight and food consumption, and corrected body weight gain was determined upon necropsy. At necropsy, dams were examined for gross pathological changes, the number of corpora lutea in the ovaries, conception rate, the number of live foetuses and pre- and postimplantation losses. The foetuses were weighed, sexed and macroscopically examined for external altera-

tions. One-half of all foetuses were fixed and examined for effects on the inner organs, while the other half of foetuses were fixed and stained for skeletal and cartilage evaluation. Dams treated at the highest dose level, 180 mg/kg body weight, exhibited the following statistically significant findings. Transient salivation for about 15 minutes was noted in 6/25 rats shortly after dosing by gavage on days 15 to 19 of gestation. This was presumably due to a bad taste and irritation of the upper digestive tract. Food consumption was decreased by 13% during the early dosing period (days 6 to 8). Body weight gain was also reduced (−45%) at this time. Evaluation of its later reduction (days 17 to 20; −34%) must also take into account the decrease in foetal weights and increase in resorptions noted at this dose level. Body weights and corrected body weights for all dose groups were similar to the control. One dam exhibited vaginal bleeding on day 20 of gestation. At necropsy, uterine weight was decreased (by 26% compared with the control group) and postimplantation loss was increased (by 43% as compared with 8% in the control) due to late resorptions. Three out of 24 dams exhibited complete resorption at the end of the treatment period and had no live foetuses. The number of live foetuses per litter was reduced. The foetal sex ratio was comparable with the control, but placental weight at 180 mg/kg body weight/day was increased by 22% relative to the control, whereas foetal weight was 14% lower than the control. The numbers of external malformations (anasarca and cleft palate) noted in 13/132 foetuses (10%) in 7/21 litters (33%) were increased compared with the control (9% and 0%, respectively). Visceral examination revealed one soft tissue malformation at this dose in the form of a misshapen unilateral kidney. Furthermore soft tissue variations in the form of dilated renal pelvis and ureters occurred (27.1% as compared with 6.4% in the control; statistically significant). Skeletal malformations were observed in 7/73 foetuses (9.6%) and 5/21 litters (24%). The respective control values were 7.8% and 1.1%. Findings included shortened scapula, bent radius, bent ulna and malpositioned and bipartite sternebrae. In addition, the number of skeletal variations (predominantly delayed ossification, 98.4% versus 91.1% in the control group) was statistically significantly increased as well as being outside the historical control incidence of the testing laboratory. A dose of 60 mg/kg body weight per day caused reduced body weight gain only on days 8 to 10 of gestation, a finding that was not considered a toxic effect. No other findings were noted. Therefore, the *no observed adverse effect level* (NOAEL) was 60 mg/kg body weight/day for both maternal toxicity

and embryotoxicity/foetotoxicity. However, the observed malformations can not be explained by the maternal toxicity of imidazole (BASF, 2002 b).

Six pregnant Wistar rats were administered by gavage a single oral dose of imidazole at 240 mg/kg body weight on day 12 or 13 of gestation (no further details). The dose was in the range of the maximum tolerated dose (no further details). Laparotomy was performed on day 22 of gestation. Two thirds of foetuses were used for skeletal examination and one third for visceral examination. Seventy live foetuses from 6 litters were available. Foetal body weight and length, the ratio of dead to live foetuses and the numbers of resorptions and corpora lutea were unaffected. There were no indications of substance-related malformations or variations/retardations (Ruddick et al., 1976).

In an in-vitro reproductive toxicity study of imidazole, rat (Sprague-Dawley-CD) embryos explanted on gestation day 10 and mouse (CD-1) embryos explanted on gestation day 8 were cultured in rat serum containing imidazole concentrations of 0 (controls), 30 or 60 µg/ml for 48 hours. Of the rat embryos, 0/8 (control), 2/10 and 3/8 died, and of the mouse embryos 0/6 (control), 2/6 and 5/6 died. Of the surviving imidazole-treated rat embryos 5/8 and 4/5 and of the mouse embryos 2/4 and 1/1 had malformations (decreased brain size, clear blisters on the caudal region of the embryo and changes in the jaw and nose regions; no further details). Furthermore, the crown-rump length was decreased in both groups of rat embryos. The number of somites and the yolk sac diameter remained unaffected by imidazole treatment (Daston et al., 1989).

From a dose level of approx. 300 µmol/kg body weight (approx. 20 mg/kg body weight), injection (no further details) of imidazole into male Sprague-Dawley rats resulted in dose-dependent decreases in testosterone concentrations in the serum and interstitial testicular fluid, in serum luteinising hormone concentrations and in interstitial testicular fluid volumes. The 1-methyl and 4-methyl derivates of imidazole and the imidazole antifungal agent ketoconazole, which were tested in parallel, were more potent on a molar basis than was the parent compound imidazole. 2-Methylimidazole was less efficacious. The investigators suspected that imidazoles could impair male fertility (Adams et al., 1998).

A 90-day oral study in Wistar rats treated at dose levels from 20 to 180 mg/kg body weight/day found no histopathological changes in the male or

female reproductive organs (see Section 7.5). Moreover, no changes were observed in the sperm parameters (testicular and epididymal sperm counts, motility and morphology) or the oestrus cycle (BASF, 2002 a).

The effect of imidazole on the sexual behaviour of male mice was studied in groups of 12 or 13 male ICR mice in behavioural tests with female mice. The animals were injected intraperitoneally with 37.5, 75, 150 or 300 mg/kg body weight 30 minutes prior to testing. Starting from the 150 mg/kg dose, imidazole caused attenuation of sexual behaviour, a finding that was in contrast to the stimulating effect observed in male rats, as reported by Ferrari et al. (1986; Mayerhofer et al., 1990).

7.9 Effects on the immune system

No information available.

7.10 Neurotoxicity

A 90-day oral study in Wistar rats treated at dose levels from 20 to 180 mg/kg body weight/day (see Section 7.5) found no treatment-related alterations in the behavioural tests (Functional Observational Battery (FOB)) or motor activity assessments. The gavage dose levels were 0 (vehicle control, water), 20, 60 or 180 mg/kg body weight/day. In addition, the brain, spinal cord and peripheral nervous system were examined by histopathology (control group and top dose group), but no treatment-related findings were noted (BASF, 2002 a).

Neuronal and non-neuronal brain cells were removed from rat foetuses on postcoital day 19 and cultured. In-vitro incubation with imidazole had no degenerative effect on the brain cells (Khera and Whalen, 1988).

7.11 Other effects

Imidazole had an analgesic and anti-inflammatory and a mild antipyretic and vasodilatory effect in animals. In addition, imidazole inhibited platelet aggregation (Italfarmaco, 1983; Pagella et al., 1983; Puig-Parellada et al., 1971, 1973; Roy et al., 1988). The pharmacodynamic effect of imidazole was probably due to the inhibition of thromboxane A2 synthetase. This resulted in decreased levels of thromboxane A_2 and a shift in cyclo-oxy-

genase metabolism, increased PGE_2 (prostaglandin E_2), PGD_2 and $PGF_{2\alpha}$ and increased prostacyclin levels (Cook et al., 1980; Engineer et al., 1978; Gordon et al., 1981; Italfarmaco, 1983; Moncada et al., 1977; Needleman et al., 1977; Pagella et al., 1983; Roy et al., 1988; Strand et al., 1981).

The ED_{50} for the inhibition of TXA_2 (thromboxane A_2) synthetase in vitro was 29.3 µg/ml. The ED_{50} determined for acetylsalicylic acid under the same conditions was 16.2 µg/ml (Pagella et al., 1983).

In another study, the ED_{50} value for the inhibition of TXA_2 synthetase was 22 µg/ml (Moncada et al., 1977).

Imidazole (100 µg/ml) inhibited the lipopolysaccharide-stimulated production of TXB_2 (thromboxane B_2) by 85.4% (from 6.38 to 0.93 ng/ml) in vitro (as determined by radioimmunoassay). The level of PGE_2 (prostaglandin E_2) in imidazole-treated macrophages was found to be 8.3 ± 7.8 ng/ml and was decreased in comparison with the lipopolysaccharide-treated control (10.6 ± 2.2 ng/ml), whereas the level of LTB_4 (leukotriene B_4), which was 431 pg/ml, was less markedly decreased by the imidazole treatment compared with the control (567 pg/ml). There was no statistically significant effect on the procoagulant activity (PCA) of alveolar macrophages obtained from New Zealand white rabbits by bronchoalveolar lavage when the macrophages were treated with imidazole (100 µg/ml) one hour before incubation with endotoxin (*Escherichia coli* lipopolysaccharide, 10 ng/ml; Williams et al., 1993).

Imidazole (30 mg/kg body weight, intraperitoneally), a known inhibitor of thromboxane biosynthesis, failed to inhibit the release of the neuropeptide calcitronin gene-related peptide (CGRP), the plasma levels of which are elevated in haemorrhagic or septic shock, in male Wistar rats (number of exposed animals unspecified) treated with bacterial endotoxin (*Salmonella enteritidis* lipopolysaccharide B; 5 mg/kg body weight, intravenously) to induce endotoxicosis. This led the investigators to conclude that thromboxane was not involved in endotoxin-induced CGRP elevations in septic shock (Wang et al., 1992, 1995).

The ED_{50} for the in-vitro inhibition of arachidonic acid-induced platelet aggregation by imidazole and acetylsalicylic acid was 55.2 and 21.6 µg/ml, respectively (Pagella et al., 1983).

Imidazole inhibited the thrombin-induced conversion of fibrinogen to fibrin in vitro at concentration levels from 21.1 to 24.5 mg/ml (Shulman, 1953).

When primary neonatal rat hepatocytes were incubated with imidazole in high-calcium medium, an increase in hepatocellular mitotic activity was observed as an increased entry into S phase (Marigo et al., 1985; Romano et al., 1988).

When human epidermal keratinocyte cultures were exposed to imidazole at a concentration of 1×10^{-3} M, the mitotic index was reduced by 41% (15.2 ± 1.5 as compared with 25.8 ± 1.0 in the control), an effect which, however, was not observed after incubation with 1×10^{-4} M (25.2 ± 3.4 as compared with 25.8 ± 1.0). Since imidazole stimulates cyclic AMP-phosphodiesterase activity in vitro leading to a decrease in cyclic AMP, the expected result would have been an increase in mitosis, so that the investigators were unable to provide an explanation for the inhibition they observed (Harper and Flaxman, 1975).

An imidazole dose of 50 mg/kg body weight, when administered intraperitoneally, quadrupled the levels of 6-keto-$PGF_{1\alpha}$, the stable metabolite of prostacyclin, and of prostaglandin E_2 in the middle cerebral artery (MCA) of the cat (Roy et al., 1988).

The analgesic effect of imidazole was investigated in the writhing test in mice. The ED_{50} values after intraperitoneal administration of imidazole ranged from 23 to 120 mg/kg body weight, depending on the substance used for induction (arachidonic acid, bradykinin, phenyl-p-benzoquinone or acetic acid). The ED_{50} values for acetylsalicylic acid obtained under the same experimental conditions were between 19 and 90 mg/kg body weight, injected intraperitoneally (Pagella et al., 1983; Puig-Parellada et al., 1973).

The anti-inflammatory effect of imidazole was investigated in the carrageenin-induced paw oedema in rats. Depending on the route of administration (oral or intraperitoneal), the respective ED_{50} values for imidazole were > 316 and 330 mg/kg body weight. The ED_{50} values for acetylsalicylic acid obtained after oral and intraperitoneal administration under the same experimental conditions were 131 and 390 mg/kg body weight, respectively (Pagella et al., 1983; Puig-Parellada et al., 1973).

The antipyretic effect of imidazole was investigated in rats by means of brewer's yeast-induced pyrexia. Imidazole had only a mild antipyretic effect (maximum effect 26%) up to an oral dose level of 200 mg/kg body weight. The ED_{50} determined for acetylsalicylic acid under the same conditions was 100.5 mg/kg body weight (Pagella et al., 1983).

When an isolated gravid guinea pig uterus was exposed to 6 mg imidazole, it reacted by contracting. The contractions intensified when another 10 mg of imidazole was added 6 minutes later. Subsequent addition of 10 mg papaverine produced relaxation of the previously strongly contracting uterus. The same effect was produced in the puerperal guinea pig uterus. The same excitatory effect on smooth muscle was also observed in the isolated rabbit intestine (no further details; Auvermann, 1918).

Ex vivo, imidazole caused contraction of the smooth muscle of the isolated guinea pig trachea and ileum and of the rat portal vein and rat uterus. The concentrations were in the range from 1 to 3.7 µM (equivalent to 0.068 to 0.252 µg/ml). Furthermore, histamine-induced contraction of the guinea pig trachea and ileum and cAMP-induced contraction of the rat uterus were statistically significantly enhanced by imidazole, as was PGE_1 (prostaglandin E_1), PGE_2 or $PGE_{2\alpha}$ induced contraction of the isolated rabbit aorta (Arunlakshana et al., 1954; Creese and Denborough, 1982; Enero, 1979; Singh and Sharma, 1984; Suzuki et al., 1982).

A 1-hour suprarenal (intra-aortic) infusion of imidazole at 50 µmol/kg body weight/minute (equivalent to 3.41 mg/kg/body weight/minute) administered to Sprague-Dawley rats (n = 7) resulted in statistically significant increases in renal plasma flow and renal arterial blood pressure by 4.35 ml/minute and by 12 mmHg, respectively. The investigators attributed this to an imidazole-induced vasodilatation. Fractional excretion of sodium, glomerular filtration rate and systemic blood pressure were not affected. Five control animals were infused with Ringer's solution (Richardson and Kunau, 1978).

Intravenous administration of imidazole at 50 µmol/kg body weight/minute (equivalent to 3.41 mg/kg body weight/minute; no details of the duration of treatment) to anaesthetised rats pretreated with normal or high dietary sodium levels (no further details) resulted in statistically significant increases in sodium excretion rate under both study conditions. This was

probably due to marked increases in urine flow rate. In addition, arterial blood pressure was significantly increased in both groups. Plasma sodium concentrations, glomerular filtration rate and renal plasma flow rate were unaffected (Baylis, 1980).

A rabbit (weighing 1900 g) given a single intravenous dose of 20 mg imidazole (equivalent to 10.5 mg/kg body weight) showed an immediate rise in blood pressure with unchanged pulse rate, which persisted for a prolonged period of time. Breathing was also recorded but showed no changes. Imidazole doses in excess of 50 mg resulted in a very marked drop in pulse rate whereas the blood pressure even rose slightly (no further details; Auvermann, 1918).

Imidazole reduced centrally mediated cardiac arrhythmias induced by intracerebroventricular microinjections of sodium glutamate or potassium chloride when the chemical itself was also administered into the lateral cerebral ventricle of anaesthetised rats. By contrast, imidazole was capable of causing cardiac arrhythmias when administered to anaesthetised rats by rapid intravenous injection. It also had no protective effect against cardiac arrhythmias induced by intravenous injection of potassium chloride (Cuparencu et al., 1986).

Intraperitoneal administration of imidazole at a dose level of 5.87 mmol/kg 4 hours prior to the subsequent experiments in isolated Langendorff-perfused hearts of male and female guinea pigs (weighing 250 to 420 g) resulted in the enhancement of cardiac arrhythmia, ventricular fibrillation and cardiac arrest induced by potassium chloride, calcium chloride or ouabain. Imidazole thus did not produce the antiarrhythmic effect seen with intracerebral administration but rather had a proarrhythmogenic effect on the heart (Filippelli et al., 1994).

Imidazole significantly reduced the threshold of electrostimulation-evoked cardiac fibrillation in the isolated guinea pig heart (Cuparencu et al., 1992).

In an older study in which imidazole was intravenously administered to guinea pigs, the agent had a protective effect against cardiac arrhythmias induced by intravenous administration of ouabain (Puig Muset et al., 1972).

Imidazole was investigated in isolated hearts from male Hartley guinea pigs to assess its cardioprotective effect against electrolysis-induced ischaemia

obtained with platinum electrodes. Imidazole failed to reduce electrolysis-induced ischaemic injury to the heart (Bullough et al., 1993).

Intraperitoneal administration of imidazole at 50 mg/kg body weight 30 minutes prior to intratracheal administration of bleomycin (10 U/kg body weight) reduced bleomycin-induced lung damage in male Sprague-Dawley rats but failed to prevent the development of interstitial fibrosis (Dussaubat et al., 1995).

The cytotoxicity (LD_{50}) of imidazole in cultured C6 rat astrocytoma cells was studied after one hour and after 4 days using trypan blue staining. The respective LD_{50} values for one-hour and 4-day exposure were 0.005 M and 0.0009 M (Mokrasch, 1990).

Intraperitoneal administration of imidazole at 200 mg/kg body weight/day for 4 days induced 2- to 4-fold increases in hepatic cytochrome P-450 levels in the rat, mouse and rabbit, but not in the hamster. This inductive effect was also demonstrated in vitro. In vivo and in vitro, the induction was characterised by increased aromatic and aliphatic hydroxylation, dealkylation and hydrolytic activity. In addition, glucuronidation reactions were increased. In contrast, a further mono-oxygenase was apparently inhibited. Intraperitoneal doses of 100 or 200 mg/kg body weight resulted in prolonged pentobarbitone- and hexobarbitone-induced sleeping times in the mouse and rat. Subcutaneous doses of 313 or 340 mg/kg body weight potentiated histamine mortality in the rat by inhibiting histaminase (diamine oxidase) activity. The inhibition was probably caused by imidazole binding to the haem iron atom (Angelakos and Loew, 1955, 1957; Butcher and Sutherland, 1962; Hajek et al., 1982; Hajek and Novak, 1982; Hoffman et al., 1989; Kaul and Novak, 1984; Kline et al., 1988 b; Koop et al., 1985; Lake et al., 1982; Miki and Yoshida, 1972; Montefiori and Kline, 1981; Olcott and Lukton, 1961; Reinke et al., 1985; Ritter and Franklin, 1987; Rowland et al., 1980; Workman et al., 1983; Zeller, 1941).

Intraperitoneal administration of imidazole to male Sprague-Dawley rats at a dose level of 250 mg/kg body weight on 3 consecutive days increased the level of ethanol-inducible cytochrome P-450j by a factor of approx. 2 without any concomitant enhancement of corresponding mRNA. Furthermore, imidazole inhibited the degradation of cytochrome P-450j in rat hepatocytes in vitro (Eliasson et al., 1988).

Male B6 mice received imidazole at 200 mg/kg body weight by the intraperitoneal route for 2 days. Liver microsomes were subsequently prepared and analysed for cytochrome P-450 and its molecular activity. Compared with structurally related enzyme inducers (e.g. pyrazole), imidazole was of intermediate efficacy (Hahnemann et al., 1989).

A study was undertaken to investigate whether in addition to cytochrome P-450 2E1, which is inducible by imidazole in the rabbit, the activity of P-450 2E2 would also be increased. To this end, newborn rabbits, in which the former enzyme is not present, were intraperitoneally treated with 400 mg/kg body weight/day for 4 days starting on day 8 of life (i.e. from day 8 to 11). On day 12, liver microsomes were prepared and examined. There was a 3-fold increase in total cytochrome P-450 content in the liver microsomes, while cytochrome b_5 and NADPH-P-450 were unchanged relative to the controls. Increases in cytochromes P-450 2E2, 1A1 and 1A2 were 3-fold, > 10-fold and > 2-fold, respectively, without any increases in the corresponding mRNA levels. The investigators suggested that these enzymes may play a role in the microsomal metabolism of certain carcinogens (Ding et al., 1992).

Imidazole induced the enzyme P-450 2E1 (a P450 isoenzyme) when incubated with liver microsomes obtained from acetone-pretreated male Sprague-Dawley rats. The extent of enzyme induction by imidazole compared with other heterocyclic compounds studied was measured as its ability to inhibit the hydroxylation of 4-nitrophenol to 4-nitrocatechol, which is catalysed by the enzyme P-450 2E1. The investigators suggested a noncompetitive mechanism for the inhibition of substrate conversion by imidazole (Hargreaves et al., 1994).

In-vitro incubation of liver microsomes from male rats with [^{14}C]-furan in the presence of NADPH resulted in the covalent incorporation of furan-derived radioactivity in microsomal protein. When imidazole was administered intraperitoneally to F344 rats at 200 mg/kg body weight/day for 4 days, there was a significant (4- to 5-fold) increase in the binding of [^{14}C]-furan to microsomal protein (Parmar and Burka, 1993).

Liver microsomes from male Wistar rats were used to study the in-vitro effect of imidazole (3 mmol) on the catalytic activity of the cytochrome P-450IIB1 and P-450IA1 enzyme systems by determining the rate of

NADPH oxidation. Induction of the metabolic rate by imidazole was greater for cytochrome P-450IA1 than for cytochrome P-450IIB1 (Yang et al., 1993).

Pancreatic enzymes (lipase, α-amylase, trypsin, chymotrypsin, elastase, carboxypeptidase B) in washings of the small intestine of albino rats were inactivated according to first-order kinetics in vitro. The enzyme inactivation was attributed in part to the bacterial activity of the intestinal microflora and microfauna. One-day incubation with various antibiotics or imidazole (0.1 M) in buffers adjusted to pH 7.4 was capable of inhibiting the development of the intestinal flora and prolonging the half-lives of the pancreatic enzymes (Khayat and Christophe, 1969).

Imidazole doses of 200 mg/kg body weight/day, when administered intraperitoneally to groups of 3 male Sprague-Dawley rats for 3 days, did not result in increased microsomal epoxide hydroxylase protein levels in liver microsomes, whereas hepatic microsomal epoxide hydroxylase mRNA levels showed a marginal (2-fold) increase. The mRNA levels of glutathione S-transferase (GSH) isoenzymes Ya, Yb1, Yc1 and Yc2 were increased 2- to 3-fold and there was a minimal increase in isoenzyme GSH Yb2 (Kim et al., 1994; Kim and Cho, 1996).

Intraperitoneal administration of imidazole at 50 mg/kg body weight/day to female albino rats for one week resulted in a statistically significant reduction in urinary ascorbic acid excretion by 7.58%. A single imidazole dose of 100 mg/kg body weight by the intraperitoneal route led to a statistically significant 27.9% reduction in ascorbic acid excretion. The reduction was maintained during further treatment of the animals with imidazole for one week. Normal ascorbic acid excretion was seen again 1 or 2 days after treatment indicating that the effect of imidazole was reversible (ascorbic acid is synthesised as a metabolite from glucose and galactose via the glucuronic acid pathway and undergoes urinary excretion; Satyanarayana et al., 1988).

A 24-hour incubation of the Hep G2 cell line with imidazole at a concentration of 45 mM caused a 50% decrease in cell protein (PI_{50} value as a measure of cytotoxicity; Dierickx, 1989).

Imidazole was capable of enhancing the catalytic activity of the serine protease plasmin in vitro (Mhashilkar et al., 1993).

When proliferating B16/C3 melanoma cell cultures were treated with androgens (testosterone, epitestosterone, 5α-dihydrotestosterone), oestradiol, oestriol or imidazole (10 mM), only imidazole was a potent inducer of the enzyme tyrosinase (which is involved in melanogenesis). The induction was inhibited by additional treatment with the above-mentioned androgens and follicular hormones (no further details; Kline et al., 1988 a, b).

Imidazole given at concentrations of 1 to 100 µg/ml had no effect on the differentiation of embryonal mouse carcinoma F9 cells. The marker protein plasminogen activator P was used as a measure of cellular differentiation after 24-hour incubation of the cells (Tanaka et al., 1995).

Intraperitoneal administration of imidazole at 200 mg/kg body weight produced statistically significant inhibition of the absorption of orally administered glucose in rats. Ten rats/dose and control group were used (Tizabi et al., 1977).

Rabbits (number of rabbits/group unspecified) with chronic intraurethral cannulation for continuous collection of urine were treated with either phenobarbitone (25 mg/kg body weight, intraperitoneally for 4 days) or imidazole (100 mg/kg body weight, intraperitoneally, single dose) and were subsequently treated with 40 mg/kg body weight oral tolbutamide. A control group received only tolbutamide, an antidiabetic agent that lowers blood glucose levels. Blood and urine samples were examined after 0, 1, 2, 4, 8, 12, 18 and 24 hours. Blood samples were analysed for tolbutamide while urine samples were analysed for tolbutamide and metabolites. Whereas phenobarbitone reduced the half-life of tolbutamide by enzyme induction and increased and accelerated its renal elimination, imidazole increased tolbutamide half-life and decreased and slowed the drug's renal excretion by inhibition of the hepatic microsomal enzymes (Visweswaram et al., 1993).

Intraperitoneal administration of imidazole at a dose level of 150 mg/kg body weight resulted in sex- and age-dependent "shaking behaviour" in Wistar rats. Males were considerably more severely affected by this change in behaviour than were females. The difference between the sexes seen after imidazole administration was no longer noted when the females were ovarectomised. The behavioural changes noted in the animals used

in these experiments were least pronounced in young animals and most pronounced in animals aged 11 to 18 weeks (Ferrari et al., 1986).

Behavioural changes were observed when imidazole was administered intraperitoneally to rats, mice and chicks. This included inhibition by imidazole of N-n-propylnorapomorphine and BHT-920 induced penile erection and stretching and yawning in rats. Apomorphine-induced hypothermia was also inhibited. Imidazole enhanced “shock”-elicited aggressiveness in rats and antagonised clonidine-induced sleep in chicks. The investigators suggested that imidazole was an antidepressant worth further investigation (Ferrari, 1985).

It has been suspected that imidazole-induced central nervous system effects observed in animals may have been caused by, *inter alia*, presynaptic α_2 receptor or dopamine blockade (Ferrari, 1985; Ferrari et al., 1986).

8 Experience in humans

For the toxicokinetics and metabolism of imidazole in humans, see Section 7.1 (Noseda et al., 1988; Kuemmerle et al., 1986).

According to the Informationsverbund Dermatologischer Kliniken (IVDK, Information Network of Departments of Dermatology for the surveillance and scientific evaluation of contact allergies in Germany), there are no hospital or literature reports of skin sensitisation in humans due to imidazole up to 1996 (IVDK, 1996).

In a production plant where contact with imidazole was possible only during sampling, product change over and filling procedures, 29 individuals were examined at the company’s occupational medicine and healthcare protection department in the context of regular medical monitoring examinations or for other reasons within the last 6.5 years. No temporary or permanent health impairments were observed in connection with exposure to imidazole. No cases of skin sensitisation were noted. As regards acute exposure and accidents with imidazole exposure, the out-patient database from 1989 to 06/1996 contained only three cases in which mild skin irritation developed after the skin was exposed to spatters or drops of the product (BASF, 1996).

When doses of 100 to 250 mg imidazole were administered to puerperal women (number unspecified) by intramuscular or intravenous injection, no discernible effect on the puerperal uterus was observed (no further details; Auvermann, 1918).

9 Classifications and threshold limit values

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area ("MAK-Kommission") has listed imidazole in the "Yellow Pages" ("Substances being Examined for the Establishment of MAK Values and BAT Values") of the List of MAK and BAT Values 2005 on the suggestion of BG Chemie in order that a MAK value be established for the chemical (DFG, 2005).

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