DOXYLAMINE SUCCINATE

1. Exposure Data

1.1 Chemical and physical data

### 1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 562-10-7
Deleted CAS Reg. No.: 121367-03-1
Chem. Abstr. Name: Butanedioic acid, compd. with *N,N*-dimethyl-2-[1-phenyl-1-(2-pyridinyl)ethoxy]ethanamine (1:1); *N,N*-dimethyl-2-[1-phenyl-1-(2-pyridinyl)-ethoxy] ethanamine, butanedioate (1:1)
IUPAC Systematic Name: Pyridine, 2-[α-[2-(dimethylamino)ethoxy]-α-methyl-benzyl]-, succinate (1:1); succinic acid, compd. with 2-[α-[2-(dimethylamino)-ethoxy]-α-methylbenzyl]pyridine (1:1)
Synonyms: Doxylamine succinate (1:1); histadoxylamine succinate

1.1.2 *Structural and molecular formulae and relative molecular mass*
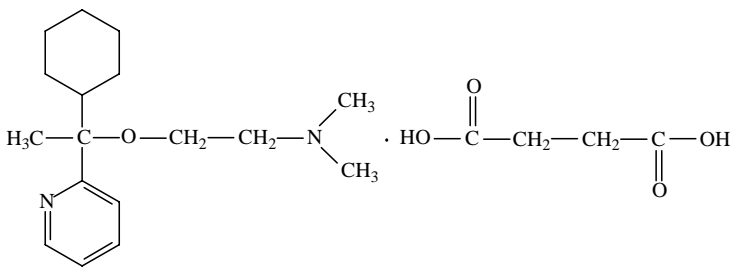
$C_{17}H_{22}N_2O.C_4H_6O_4$ Relative molecular mass: 388.46

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: White or creamy-white powder (Gennaro, 1995)
(*b*) *Melting-point*: 100–104 °C (Budavari, 2000)

(c)   *Solubility*: Very soluble in water (1000 g/L at 25 °C) and chloroform; soluble in ethanol; slightly soluble in benzene and diethyl ether (Gennaro, 1995; American Hospital Formulary Service, 2000; Budavari, 2000)

(d)   *Spectroscopy data*: Infrared [proton (9383), grating [45206P] spectral data have been reported (Sadtler Research Laboratories, 1980).

(e)   *Ionization constants*: pKa, 5.8 and 9.3 (American Hospital Formulary Service, 2000)

1.1.4   *Technical products and impurities*

Doxylamine is currently formulated exclusively as the succinate salt. Doxylamine succinate is commercially available as an over-the-counter 25-mg tablet and a 50-mg liquid-filled capsule; it is also available in combination with antitussives and decongestants. Inactive ingredients in commercial formulations may include dibasic calcium phosphate, FD&C Blue No. 1, aluminium lake, magnesium stearate, microcrystalline cellulose and sodium starch glycolate (Gennaro, 1995; American Hospital Formulary Service, 2000; Medical Economics Co., 2000).

Trade names for doxylamine succinate include Alsadorm, Decapryn, Donormyl, Dormacil, Dormidina, Doxised, Doxy-Sleep-Aid, Dozile, Duebien, Evigoa D, Gittalun, Hewedormir, Hoggar N, Lidène, Mereprine, Munleit, Nighttime Sleep Aid, Noctyl, Nytol, Restaid, Sanalepsi, SchlafTabs-ratiopharm, Sedaplus, Sleep Aid, Sleep Easy and Unisom (Royal Pharmaceutical Society of Great Britain, 2000; Swiss Pharmaceutical Society, 2000; Vidal, 2000).

Doxylamine succinate is also used in over 50 pharmaceutical preparations in combination with other drugs.

1.1.5   *Analysis*

The *US Pharmacopeia* specifies ultraviolet absorption spectrophotometry with comparison to standards as the method for identifying doxylamine succinate; titration with perchloric acid is used to assay its purity. In pharmaceutical preparations, doxylamine succinate is identified by infrared absorption spectrophotometry; ultraviolet absorption spectrophotometry and high-performance liquid chromatography are used to assay for content (US Pharmacopeial Convention, 1999).

1.2   Production

Doxylamine can be prepared by converting methylphenyl-2-pyridylcarbinol into its sodium alcoholate and refluxing in toluene or in the presence of sodamide in xylene with 2-(*N,N*-dimethylamino)ethyl chloride. The doxylamine thus formed is converted to its succinate salt by reaction with an equimolar quantity of succinic acid in warm acetone (Gennaro, 1995; Budavari, 1998).

Information available in 2000 indicated that doxylamine succinate was manufactured by three companies in Germany and one company each in Ireland, Italy, Mexico and Spain (CIS Information Services, 2000a).

Information available in 2000 indicated that doxylamine succinate was used in the formulation of pharmaceuticals by 12 companies in South Africa, nine companies in Germany, seven companies in Spain, six companies in India, five companies in Australia, four companies each in Brazil, Canada, Taiwan and the United Kingdom, three companies in Chile, two companies each in Egypt, France, the Republic of Korea, Switzerland, Turkey and the USA and one company each in Indonesia, Thailand, Philippines and Venezuela (CIS Information Services, 2000b).

1.3   Use

Doxylamine succinate, an ethanolamine-based antihistamine, shares the actions and uses of other antihistamines. Because of its sedative effect, it is used in the short-term management of insomnia. It is used for the symptomatic relief of hypersensitivity reactions and in the treatment of pruritic skin disorders. It is also used in combination with antitussives and decongestants (e.g., dextromethorphan, pseudoephedrine, phenyl-propanolamine) for the temporary relief of cough and cold symptoms (Gennaro, 1995; American Hospital Formulary Service, 2000; Medical Economics Co., 2000; Royal Pharmaceutical Society of Great Britain, 2000).

Since 1956, doxylamine succinate has been used in the management of nausea and vomiting during pregnancy, in combination with pyridoxine hydrochloride and dicyclomine hydrochloride until the mid-1970s (Reynolds, 1996) and then in combination with pyridoxine alone until the early 1980s in most countries. The combination drug was known as Bendectin® or Debendox®. A formulation known as Diclectin® is apparently still available in Canada (Mitchell *et al*., 1983; Tyl *et al*., 1988; Royal Pharmaceutical Society of Great Britain, 2000).

The usual oral dose of doxylamine succinate as an antihistamine for adults and children 12 years and older is 7.5–12.5 mg every 4–6 h, not to exceed 75 mg within 24 h. Under the direction of a physician, these patients may receive up to 25 mg every 4–6 h [or 2 mg/kg bw or 60 mg/m² daily in divided doses], not to exceed 150 mg within 24 h. The usual oral dose for children 6–12 years old is 3.75–6.25 mg every 4–6 h, not to exceed 37.5 mg within 24 h. Under the direction of a physician, these paediatric patients may receive up to 12.5 mg every 4–6 h [or 2 mg/kg bw or 60 mg/m² daily in divided doses], not to exceed 75 mg within 24 h. Under the direction of a physician, children aged 2 to < 6 years may receive an antihistaminic dose of 1.9–3.125 mg every 4–6 h, not to exceed 18.75 mg in 24 h. The drug is contraindicated for neonates (Gennaro, 1995; American Hospital Formulary Service, 2000).

1.4   Occurrence

No data were available to the Working Group.

1.5   Regulations and guidelines

Doxylamine succinate is listed in the pharmacopoeias of France, Germany and the USA (US Pharmacopeial Convention, 1999; Royal Pharmaceutical Society of Great Britain, 2000; Swiss Pharmaceutical Society, 2000; Vidal, 2000). It is also registered for human use in Ireland, Italy, Portugal, Spain and the United Kingdom (Instituto Nacional de Farmacia e do Medicamento, 2000; Irish Medicines Board, 2000; Medicines Control Agency, 2000; Ministry of Health, Department of Drugs Assessment and Monitoring, 2000; Spanish Medicines Agency, 2000).

2.   Studies of Cancer in Humans

2.1   Case report

In a series of 200 children included in a case–control study of primary intracranial neoplasm, the authors mention 'the surprising coincidence' of two girls with a posterior fossa pilocytic astrocytoma whose mothers had taken Bendectin® [which contains doxylamine, dicyclomine and pyridoxine] (Giuffrè *et al*., 1990).

2.2   Case–control studies

In a study of childhood cancer in England, 615 cases and 1230 controls were considered to be eligible for the study (Birch *et al.*, 1985). The parents of 555 children (response rate, 90%) in whom an incident cancer (171 leukaemias, 74 lymphomas, 78 central nervous system tumours and 232 other cancers) had been diagnosed in the regional paediatric oncology clinics of three Health Service regions of England were interviewed (McKinney *et al*., 1985). For each case, two controls matched on age and sex were selected, one on the list of the same general practitioner as the case child and the other from paediatric hospital admissions, with response rates of 72% and 64%, respectively. Controls who refused to participate were replaced, to obtain a total of 1110 controls. Information on the drug use of the mother during pregnancy was obtained by interview and also, whenever possible, from the combined information from obstetric records (88%) and general practitioners' notes (91%). The odds ratio for all cancers associated with use of Debendox® during pregnancy as reported by the mother was 0.69 and that obtained from medical records was 0.99. Although the odds ratio was significantly increased in relation to medically recorded use for 1–2 months (odds ratio, 10; 95% confidence interval [CI], 1.8–57), there was no dose–response relationship, the odds

ratios being 0.75 for 2–6 months' use and 0.50 for > 6 months. The odds ratios for use of Debendox® reported by the mother were below 1 for any duration of use. For the group of leukaemias and lymphomas combined, the odds ratio was 1.0 with both exposure ascertainment methods, and those for other cancers were 0.47 with the mothers' recall and 0.95 with medical records.

A case–control study was conducted on patients under 18 years in the member and affiliate institutions of the Children Cancers Study Group in Canada and the USA in whom acute non-lymphoblastic leukaemia had been diagnosed between 1980 and 1984 (Robison *et al.*, 1989). For each case, one control was selected by random-digit dialling and matched on age, race and telephone area code. Of the 262 eligible patients, 204 (78%) were interviewed, as were 78% of the 260 eligible controls. The two parents were interviewed separately by telephone on a wide range of topics. The matched-pair odds ratio for maternal use of Bendectin® or other tablets for morning sickness during pregnancy was 1.8 (95% CI, 0.98–3.2), although the mothers of patients did not report morning sickness more frequently than mothers of controls (odds ratio, 0.80). The risk increased with increasing duration of use ($p = 0.05$; test for trend), and the odds ratio for use for more than 10 weeks compared with less than 1 week was 2.8 ($p < 0.05$).

3.   Studies of Cancer in Experimental Animals

3.1   Oral administration

Mouse: Groups of 48 male and 48 female B6C3F$_1$ mice, 31–40 days of age, were fed diets containing doxylamine succinate (purity, 100%) at a concentration of 0, 190, 375 or 750 mg/kg (dose based on the free amine) for 104 weeks. Additionally, groups of 12 males and 12 females were fed the same concentrations for 65 weeks, at which time all surviving animals were killed. The survival rates in each group at the end of 104 weeks varied from 88 to 96% for males and from 85 to 98% for females. Increased incidences of hepatocellular adenoma were seen in both males (6/60 control, 12/60 low dose, 17/59 mid dose ($p < 0.01$; Fisher's exact test) and 31/60 high dose ($p < 0.001$)) and females (0/58, 3/60, 0/60 and 9/60 ($p < 0.01$), respectively). Thyroid follicular-cell adenomas were observed in both males (1/58, 0/57, 11/57 ($p < 0.01$) and 5/58) and females (0/56, 0/60, 2/57 and 8/59 ($p < 0.01$)). Dose-related increases in the incidence of follicular-cell hyperplasia were also observed in both male and female mice (Jackson & Sheldon, 1993).

Rat: Groups of 48 male and 48 female Fischer 344 rats, 31–40 days of age, were fed diets containing doxylamine succinate (purity, 100%) at a concentration of 0, 500, 1000 or 2000 mg/kg (dose based on the free amine) for 104 weeks. Additional groups of nine males and nine females received the same concentrations for 65 weeks, at which time animals were killed. The survival rates in each group at 104 weeks varied from 40 to 58% in males and from 56 to 69% in females. When compared with

controls, the final body weight of high-dose males was reduced by 8.4% and that of females by 22.8%, suggesting that the maximal tolerated dose had been exceeded for the females. The incidence of hepatocellular adenoma and carcinoma combined in males was: control, 0/57; low dose, 0/57, mid dose, 0/57 and high dose, 5/57 ($p \leq 0.05$; Fisher's exact test). The five liver tumours in males at the high dose comprised two adenomas and three carcinomas. There was no increase in the incidence of neoplasms in female rats (Jackson & Blackwell, 1993).

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

4.1   Absorption, distribution, metabolism and excretion

4.1.1   *Humans*

The pharmacokinetics of doxylamine succinate was determined in 16 healthy male volunteers after administration of a single oral dose of 25 mg. The mean peak plasma concentration was 99 ng/mL, the peak time was 2.4 h after the dose, the elimination half-time was 10.1 h, and the apparent oral clearance was 217 mL/min (Friedman & Greenblatt, 1985). Clearance of a single oral dose of 25 mg of doxylamine succinate was slower (174 versus 240 mL/min) in older men (60–87 years) than in younger men (20–43 years), but no difference was seen in women (Friedman *et al.*, 1989).

N-Desmethyldoxylamine, *N,N*-didesmethyldoxylamine and their respective *N*-acetyl conjugates were identified as urinary metabolites after oral administration of 50 mg of doxylamine succinate to a single volunteer (Ganes & Midha, 1987). Approximately 1% of an oral dose of 75–100 mg of doxylamine succinate was recovered in the urine of male volunteers as quaternary ammonium-linked glucuronides (Luo *et al.*, 1991).

4.1.2   *Experimental systems*

Total urine and faecal recovery of radiolabel after oral administration of [^{14}C]-doxylamine succinate at 13.3 or 133 mg/kg bw to male and female Fischer 344 rats was > 90%, regardless of sex and dose. The identified unconjugated urinary metabolites (representing 36–44% of the radiolabel) included doxylamine *N*-oxide, *N*-desmethyl-doxylamine, *N,N*-didesmethyldoxylamine and ring-hydroxylated products of doxyl-amine and desmethyldoxylamine (Holder *et al.*, 1987). The identified conjugated meta-bolites (representing 44–55% of the radiolabel) included doxylamine *O*-glucuronide, *N*-desmethyldoxylamine *O*-glucuronide and *N,N*-didesmethyldoxylamine *O*-glucu-ronide (Holder *et al.*, 1990). *N*-Acetyl conjugates of *N*-desmethyl- and *N,N*-dides-methyldoxylamine were tentatively identified in rat urine (Ganes *et al.*, 1986).

[14]C-Doxylamine succinate given as a single oral dose of 13 mg/kg bw to four female rhesus monkeys (*Macaca mullata*) was metabolized by at least four pathways: a major pathway to mono- and didesmethyldoxylamine via successive *N*-demethylation; a major pathway to side-chain cleavage products via direct side-chain oxidation and/or deamination; a minor pathway to the *N*-oxide; and a minor pathway to unknown polar metabolites (Slikker *et al.*, 1986). In two male squirrel monkeys (*Saimiri sciureus*) given 20 mg of doxylamine succinate orally twice daily for 1 week, only the *N*-acetyl conjugate of *N,N*-didesmethyldoxylamine was detected in the urine (Ganes *et al.*, 1986). Repeated oral administration of 7 mg/kg bw per day of Bendectin® during days 22–50 of gestation to three cynomolgus monkeys (*Macaca fascicularis*), four rhesus monkeys (*Macaca mulatta*) and five baboons (*Papio cynocephalus*) did not alter the pharmacokinetics of doxylamine (Rowland *et al.*, 1989).

Analysis of fetal plasma samples by high-performance liquid chromatography demonstrated the presence of doxylamine and metabolites after a single intravenous injection of 13.3 mg/kg bw doxylamine succinate to three rhesus monkeys in late-term pregnancy (Slikker *et al.*, 1987, 1989).

4.1.3   *Comparison of animals and humans*

Similar demethylated metabolites and their *N*-acetylated derivatives have been determined in the urine of humans, monkeys and rats after oral doses of doxylamine succinate. In addition, rats metabolized the compound by *N*-oxidation, aromatic hydroxylation and ether cleavage.

4.2   **Toxic effects**

4.2.1   *Humans*

In 109 cases of intoxication with doxylamine preparations, the most frequent symptoms included impaired consciousness, seizures, tachycardia, mydriasis and a psychosis-like state similar to catatonic stupor. A serious complication may be rhabdomyolysis with subsequent impairment of renal function and acute renal failure (Köppel *et al.*, 1987).

4.2.2   *Experimental systems*

Administration of feed containing doxylamine succinate at a concentration of 0, 40, 375, 750 or 1500 mg/kg (expressed as free amine) to male and female $B6C3F_1$ mice for 7 or 15 days resulted in decreased serum thyroxine concentrations (approximately 80% of control) with compensatory increases (fourfold) in those of serum thyroid stimulating hormone, as also seen with phenobarbital at a concentration of 375 mg/kg of diet (expressed as free acid). No clear changes in serum triiodothyronine concentration were apparent (Bookstaff *et al.*, 1996).

Groups of 12 male and female Fischer 344 rats were given diets containing doxyl-amine succinate at a concentration of 0, 162, 405, 1012, 2530 or 6325 ppm (expressed as free amine) for 90 days. The only histopathological changes seen were cytoplasmic vacuo-lization or fatty change in the liver and cytomegaly in the parotid salivary glands (Jackson & Blackwell, 1988a). In groups of 12 male and female B6C3F$_1$ mice given diets containing doxylamine succinate at a concentration of 0, 80, 162, 325, 750 or 1500 ppm (expressed as free amine) for 90 days, the liver was the only organ affected. The histological lesions consisted of mild to severe cytomegaly and/or karyomegaly and a high incidence of hepatocellular necrosis in animals of each sex at the highest concentration in feed, although necrosis was also observed at lower concentrations (Jackson & Blackwell, 1988b)

4.3   Reproductive and developmental effects

4.3.1   *Humans*

Doxylamine succinate has rarely been used on its own, but it has been used exten-sively in pregnancy in combination with pyridoxine as Bendectin® for the treatment of nausea and vomiting. Reviews of the extensive literature on Bendectin® use, covering many thousands of women exposed during pregnancy, have concluded that the drug is not a human teratogen (Shiono & Klebanoff, 1989; McKeigue *et al.*, 1994; Brent, 1995).

4.3.2   *Experimental systems*

No satisfactory studies on doxylamine alone were available to the Working Group. Studies of Bendectin® in rats and non-human primates were available.

Groups of 37–41 pregnant CD Sprague–Dawley rats were given 0, 200, 500 or 800 mg/kg bw Bendectin® by gavage daily on days 6–15 of gestation (day 0 being considered that on which a positive vaginal smear was found) and were killed on day 20 for examination of their fetuses by standard teratological techniques. The highest dose was very toxic to the dams, killing 17%, and a marked reduction in body-weight gain was observed at the two higher doses. The lowest dose was minimally toxic. A small increase in the frequency of resorptions was seen at the highest dose and reduced fetal weight and reduced skeletal ossification at 500 and 800 mg/kg bw per day. There was no increase in the number of fetuses with malformations, but the number of litters with malformed fetuses was increased at the highest dose, due mainly to an increase in the number of fetuses with short 13th ribs. No increase in the incidence of external or visceral malformations was observed in any group (Tyl *et al.*, 1988).

Groups of 21–24 pregnant cynomolgus monkeys (*Macaca fascicularis*) were given Bendectin® at an approximate dose of 0, 1.3, 3.3 or 13.3 mg/kg bw (as 2/5, 1 and 4 tablets/day per animal, corresponding to two, five and 20 times the human dose) by nasogastric intubation daily on days 22–50 of gestation. The fetuses were removed

surgically just prior to term for examination. No maternal toxicity and no embryofetal toxicity or teratogenicity was observed (Hendrickx *et al.*, 1985).

4.4 Effects on enzyme induction or inhibition and gene expression

4.4.1 *Humans*

A randomized, placebo-controlled study was conducted in 48 healthy male volunteers to compare the effects of doxylamine succinate on the pharmacokinetics of antipyrine metabolites and the urinary excretion of 6β-hydroxycortisol. Normal renal function, an age between 18 and 40 years and a normal diet were the criteria for inclusion. Groups of 16 men received 12.5 mg of doxylamine succinate, placebo or 30 mg of phenobarbital orally every 6 h for 17 days. No statistically significant differences indicative of enzyme induction were observed (Thompson *et al.*, 1996).

4.4.2 *Experimental systems*

Doxylamine succinate caused a dose-dependent increase (up to 2.6-fold) in liver microsomal cytochrome P450 (CYP) enzyme activity in male and female $B6C3F_1$ mice (aged 45–52 days) after 7 or 15 days on a diet containing the compound at a concentration of 0, 40, 375, 750 or 1500 mg/kg (expressed as free amine). Doxylamine succinate caused marked induction of CYP2B enzymes, as demonstrated by a large increase in the *O*-dealkylation of 7-pentoxyresorufin (up to 38-fold) and in the 16β-hydroxylation of testosterone (up to 6.9-fold). In addition, treatment resulted in a modest induction of CYP3A and CYP2A and a 50% increase in thyroxine glucuronosyltransferase activity. No induction of CYP1A, CYP2E or CYP4A was found. These results suggest that doxylamine is a phenobarbital-type inducer of liver microsomal CYP enzymes in $B6C3F_1$ mice (Bookstaff *et al.*, 1996).

Doxylamine inhibited aminopyrine *N*-demethylation by rat liver microsomes, with a median inhibitory concentration of 73 μmol/L (Brandes *et al.*, 1994).

4.5 Genetic and related effects

4.5.1 *Humans*

No data were available to the Working Group.

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

Doxylamine succinate did not induce mutations in *Salmonella typhimurium*. It weakly induced unscheduled DNA synthesis in primary rat hepatocytes *in vitro* in the absence of an exogenous metabolic system. It inhibited gap-junctional intercellular communication, measured as metabolic cooperation, in Chinese hamster V79 cells. It

Table 1. Genetic and related effects of doxylamine succinate

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Salmonella typhimurium TA100, T1535, TA1537, TA98, reverse mutation	–	–	10 000 µg/plate	Zeiger *et al* (1987)
Unscheduled DNA synthesis, Fischer 344 primary rat hepatocytes *in vitro*	(+)	NT	194	Budroe *et al.* (1984)
Inhibition of gap-junctional intercellular communication, Chinese hamster V79 cells *in vitro*	+	NT	80	Toraason *et al.* (1992)
Sister chromatid exchange, human lymphocytes *in vitro*	–	–	15 930	Müller *et al.* (1989)
Micronucleus formation, Chinese hamster bone marrow *in vivo*	–		400 po × 1	Müller *et al.* (1989)
Chromosomal aberrations, transplacental exposure, NMRI mouse embryo *in vivo* (whole-body suspension)	+		150 po × 1	Müller *et al.* (1989)
Sister chromatid exchange, transplacental exposure, NMRI mouse embryo *in vivo* (whole-body suspension)	–		300 po × 1	Müller *et al.* (1989)
Micronucleus formation, transplacental exposure, fetal blood, NMRI mice *in vivo*	–		300 po × 1	Müller *et al.* (1989)

[a] +, positive; (+), weak positive; –, negative; NT, not tested; po, orally
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw per day

did not induce sister chromatid exchange in human lymphocytes *in vitro* or micro-
nucleus formation in hamster bone-marrow cells. In a transplacental system, a small
dose-dependent induction of chromosomal aberrations, but no sister chromatid
exchange or micronucleus formation, was found in the embryos of mice treated on day
11 of gestation[1].

4.6   Mechanistic considerations

Doxylamine succinate is considered not to be genotoxic.

It is a potent phenobarbital-type inducer of hepatic CYP2B enzymes in $B6C3F_1$
mice. In contrast, male volunteers given doxylamine succinate repeatedly showed no
evidence of CYP enzyme induction. Doxylamine succinate, like phenobarbital, also
induced thyroxine glucuronosyltransferase activity in mice, accompanied by decreased
serum concentrations of thyroxine and increased serum concentrations of thyroid-
stimulating hormone.

The lack of increased activity of liver enzymes associated with thyroxine meta-
bolism and the increased thyroid-stimulating hormone concentrations in humans
exposed to doxylamine succinate for longer than therapeutically recommended indicate
that the compound would not be expected to produce thyroid tumours in humans at
therapeutic doses. Doxylamine succinate damaged the liver in mice, and this effect may
be related to its hepatocarcinogenicity.

5.   Summary of Data Reported and Evaluation

5.1   Exposure data

Doxylamine succinate is an ethanolamine-based antihistamine used in the
management of insomnia and, in combination with antitussives and decongestants, in
the relief of cough and cold symptoms. It was widely used until the early 1980s in
combination with other drugs to control nausea associated with pregnancy and is still
registered for this use in at least one country.

5.2   Human carcinogenicity data

Two studies addressed the association between use of an anti-emetic drug
containing doxylamine succinate during pregnancy and cancer during childhood in the
offspring. The study in England showed no association with childhood cancer in

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[1] The Working Group was aware of unpublished studies of sister chromatid exchange and chromosomal
aberrations in Chinese hamster ovary cells *in vitro*, which showed no effect of doxylamine succinate.

general or with lymphohaematopoietic neoplasms, and no evidence of a dose–response relationship. The study from Canada and the USA on children with acute non-lympho-blastic leukaemia found an increased risk of borderline significance for self-reported use of a drug containing doxylamine succinate or other tablets for morning sickness during pregnancy and a trend of borderline significance with duration of use.

5.3   Animal carcinogenicity data

Doxylamine succinate was tested by oral administration in one study each in mice and rats. In mice, it increased the incidences of hepatocellular and thyroid follicular-cell adenomas in males and females, although the thyroid response was not dose-related in males. In rats, doxylamine succinate marginally increased the incidence of hepatocellular adenomas and carcinomas combined only in males.

5.4   Other relevant data

Doxylamine is converted to demethylated metabolites and their *N*-acetylated derivatives in humans, monkeys and rats. In rats, doxylamine is also metabolized via *N*-oxidation, aromatic hydroxylation and ether cleavage pathways. Doxylamine is a potent, phenobarbital-type inducer of cytochrome P450 enzymes in mice. No evidence of enzyme induction has been found in humans. Doxylamine succinate causes liver damage in mice; this effect may be related to its hepatocarcinogenicity. Doxylamine induces thyroxine glucuronidation in mice, with concomitant decreases in serum thyroxine and increases in serum thyroid stimulating hormone concentrations. This is the probable mechanism of action for the induction of thyroid tumours in animals. It has not been shown to be teratogenic in humans or experimental animals.

No data were available on the genetic and related effects of doxylamine succinate in humans. It did not induce micronucleus formation in mice when given trans-placentally or in hamsters. It did, however, induce chromosomal aberrations in mice treated transplacentally. Doxylamine succinate induced DNA damage in primary rat hepatocytes and inhibited intercellular communication, but it did not induce sister chromatid exchange in mammalian cells in culture or induce mutations in bacteria. Doxylamine succinate is considered not to be genotoxic.

5.5   Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of doxylamine succinate.

There is *limited evidence* in experimental animals for the carcinogenicity of doxylamine succinate.

Overall evaluation

Doxylamine succinate is *not classifiable as to its carcinogenicity to humans (Group 3)*.

6.   References

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