UNDATED

Sec - Butylamine

Identity

Chemical Name: 2-amino butane

Sec - butylammonium acetate (phosphate)

Symonyms: Tutane®

Structural Formula: $Bu^s NH_2 (CH_3COOH)$

$CH_3CH_3CHNH_2CH_3 (CH_3COOH)$

Empirical Formula: $C_4H_{11}N (C_2H_4O_2)$

Molecular Weight: 73

Other Information on Identity and Properties:

Colorless liquid

Ammoniacal odor

B.P. 63°C

V.P. 135 mm Hg @20°C

N_D^{20} 1.394

d_4^{20} 0.724

Organic base forming water soluble salts with acids.

Exists as optical isomers (d-isomer=active)

Corrosive to some metals

Reactants in Manufacture:

Composition of Technical product

EVALUATION FOR ACCEPTABLE DAILY INTAKE

Biochemical Aspects

Biotransformation

Urinary samples from two days treated daily with 5000 ppm or 10,000 ppm were acidified and distilled. A diphenyl hydrozon was formed which corresponded to the product formed from a reaction with methyl ethyl ketone. Methyl ethyl ketone formed from the deamination of Sec-butylamine and appeared to be excreted. The amine nitrogen entered the biological pool and was lost (Worth and Meyers, 1965).

Distribution and Elimination

Studies were carried out on the distribution of Sec-butylamine in edible tissues, milk and excretory products of cows. Sec-butylamine is apparently rapidly absorbed as evidenced by its presence in milk at 3 days after feeding. The 2-3 day interval was the first assayed and the level from that time on for the remainder of a feeding trial was constant.

Residues of Sec-butylamine were found in muscle, liver, fat and kidney in a dose relationship at 100 and 10 ppm (but not 2 ppm) levels in the diet fed to cows for up to 28 days. The residues were found in samples taken at 0 withdrawal time after feeding (animals were fed diets containing Sec-butylamine until sacrificed). Data on the presence of Sec butylamine in urine and feces suggest that it is readily absorbed into the blood and excreted primarily in the urine (Anon, 1975).

No definitive metabolism studies have been performed.

Toxicological Studies

Special Studies

Reproduction - Rat

Groups of rats (20 males and 20 female rats per group) were fed Sec-butylamine acetate at levels of 0, 500 and 2500 ppm in a two litter per generation, 4 generation reproduction study. The Fo parents were allowed to bear 6 additional litters. The F1b, 2b and 3b litters were used as parents for the following generation and maintained for varying periods (162-202 days after weaning their respective litters). Reproduction indices, fertility index, gestation index, viability index and lactation index, were normal. A reduction of growth was noted throughout the study at the high dietary level. Reproduction was unimpaired for any of the 8 litters produced by the Fo generation (Worth, et al, 1969a).

Rabbit

Groups of rabbits were fed Sec-butylamine phosphate in the diet and subjected to a two generation, one litter per generation reproduction study. Two groups of rabbits (10 males and 14 females in the treatment group; 5 males and 10 females in the control group) were fed for 53-54 days and the females artificially inseminated with semen collected from two control and two treated males. The dietary levels were 0 and 2500 ppm. The F1a were maintained for six months divided into groups of 6 males and 12 females fed 2500 ppm Sec-butylamine phosphate with 5 males and 8 females fed control diets. These animals were bred by insemination, allowed to bear young, maintained for 63 days and discarded. On postpartum day 14 and day 28 milk samples were taken and analyzed for Sec-butylamine.

Mortality of several rabbits was evident at an original dose level of 5000 ppm. After the rabbits on this level were switched to the 2500 ppm regimen, mortality and growth of all animals was normal. The dietary level of 2500 ppm had no effect on fertility, duration of gestation delivery of live progeny or lactation indicies in both generations examined. Growth of progeny in the F1 generation was normal while it was slightly depressed in the F2. There were no effects noted on survival of offspring in either generation. There was a constant level of Sec-butylamine found in milk at both the 14 and 28 days ranging from 20 to 77 ppm in the F1 and 19 to 84 in the F2. [The analytical method used in the study is sufficient to detect Sec-butylamine in milk but the sensitivity is questionable as food samples containing 2500 ppm were found to contain 1770-1820 ppm or a recovery of 72%. The procedure is sufficient to suggest that the F1 and F2 generation were exposed to the pesticide from parturition]. The presence of 2500 ppm Sec-butylamine in the diet had no effect on reproduction in the rabbit (Gibson et al, 1970).

Teratology

Groups of Dutch Belted does (10 rabbits/group) were administered Sec-butylamine acetate at a dose of 0, 75 and 150 mg/kg daily from day 8 thru day 18 of gestation. On day 28 the does were sacrificed and half of the fetuses were examined for gross and skeletal abnormalities. Half of the fetuses were incubated for 24 hours to assess viability after which they were examined and discarded. Mean fetal weight appeared lower than controls and a decreased viability of live fetuses were noted at the

high dose level. There were no differences from controls with respect to reproduction, sex distribution of fetuses or in the number of malformations observed (Worth, et al 1966).

Acute Toxicity

Species	Route	LD50 (mg/kg)	Chemical Form	Reference
Mouse	Oral	660	base	Worth & Anderson, 1965
		1750-2470	salt*	"
	IV	225	base	"
Rat	Oral			
Newborn		350	base	"
Weanling		350	base	"
Adult		380	base	"
Newborn		430-690	salt*	"
Weanling		1270-1660	salt*	"
Adult		1510-4600	salt*	"
	Inhalation	3.5 mg/L	salt & base*	"
Guinea Pig	Oral	880	salt*	"
Dog	Oral	250	base	"
		250-500	salt*	
Rabbit	Dermal	2500	base & salt*	"

*Little differences were noted in 4 salt forms (acetate, phosphate, carbonate, and HCl) and the range for these is presented.

Signs of poisoning in rat included salvation for 2 hours before convulsion. In rats and mice acute gastritis, excessive mucus secretion and respiratory paralysis were noted. In dogs foamy bloody vomitus, depression tremors and mydriasis were observed. In primary dermal irritation studies, salts of Sec-butylamine were non-irritating while the base administered at 0.7 ml/animal was a primary irritant.

Pharmacologic Response

Groups of dogs were administered Sec-butylamine as the carbonate or acetate salt and data were recorded on heart rate, respiration rate, blood pressure and with an EKG apparatus. Intravenous administration of either the acetate or carbonate resulted in elevated blood pressure, heart rate and respiration, Intragastric administration of larger doses resulted in similar responses. It was suggested that the primary acute response is similar to other amines producing a standard sympathomimetic response (Worth and Henderson, 1965).

Short Term Studies

Groups of rats (10 male and 10 female rats per group) were fed Sec-butylamine acetate in the diet for 3 months at levels of 0, 312.5, 625, 1250, 2500 and 5000 ppm. A significant growth reduction was noted at 5000 ppm. A dose dependent leukopenia in both males and females was recorded although no other effects on clinical chemistry parameters were observed. Gross and microscopic examination of tissues and organs showed no adverse effects of dietary Sec-butylamine (Worth, et al 1965).

Groups of mongrel dogs (2 male and 2 female dogs per group) were administered Sec-butylamine acetate by capsule for 91 days at levels equivalent to 0, 1250, 2500 and 5000 ppm of the diet. [No indication of whether treatment was for 5 or 7 days/week]. No effects were noted in this study on growth (body weight stability), hematology, clinical chemistry or gross and microscopic examination of tissues and organs (note report of microscopic examination tables B8-80 is absent although gross report; table B7 is present) (Worth, et al 1965).

animals. Two other deaths occurred (one male at 62.5 mg/kg and one male at 125 mg/kg) apparently not attributable to the Sec-butylamine acetate. Abnormal behavior was not observed in any treatment. Body weights at the termination of the study were normal in all animals including those dogs fed 10,000 ppm in the diet. Keratitis was observed in 3 of 4 dogs fed 10,000 ppm. Hematology values were normal except for a reduced hemoglobin and hematocrit value (especially in females) at 10,000 ppm. Urinalysis and clinical chemistry values were unaffected. Gross examination of tissues and organs indicated increased kidney weight and decreased spleen weight in females at 10,000 ppm. Leukocyte counts were normal as were bone marrow m/e ratios. Microscopic examination of tissues and organs showed no pathological conditions. A no effect level in this study is 125 mg/kg body weight/day (Worth, et al 1969b).

Long Term - Rat

Groups of rats (30 males and 30 females per group) were fed Sec-butylamine acetate in the diet for 2 years at dose levels of 0, 1250, 2500 and 5000 ppm. Survival of rats over the two years was not affected by Sec-butylamine acetate. Terminal body weight was slightly reduced in males at 5000 ppm. Hematological findings recorded at several intervals over the test period were normal. Leukocyte count averages at the end of the study were normal but the range of values suggested a possible leukopenia at 5000 ppm. Terminal male kidney weight was increased while prostate and testes were reduced. These changes were

not evident in female kidney, ovary or uterus. [A finding of "light cell" ademona of the thyroid in treated animals was reported. A higher incidence in 5000 ppm rats may be due to the higher incidence of survival at this level and does not appear to be significant. There are no data of the incidence of this in animals not surviving to the end of the study. This note for information only - not for inclusion in monograph]. Gross and microscopic examinations of tissues and organs, except where noted above, were normal. A no effect level for this study is 2500 ppm (Worth, et al 1969b).

OBSERVATIONS IN MAN

None

[No definitive studies have been reported. A series of letters from industrial users of the material have been offered as suggestions that although occupational exposure is present, the hazard is low].

Comments

Sec-butylamine (S-BA) is an agricultural fungicide formulated currently as the phosphate salt. S-BA is absorbed through the GI tract and distributed widely in the body. An equilibrium level in body tissues milk and excreta is apparent after 2-3 days feeding high dietary levels. Excretion into milk is apparent and may be a source of concern to the Meeting. It has been suggested that this simple molecule is degraded by oxidative deamination resulting in methyl ethyl ketone and N_2 in the amine pool of the body. Tissue and milk residue dissipation studies are not available and all data reported on these residues are from animals sacrificed at zero time after feeding diets containing S-BA.

Several reproduction studies in rats and rabbits including a study for teratological potential were negative. Reproduction was unimpaired over a 4 generation rat reproduction study and a 2 generation rabbit study - including a study of 8 litters from the parents of the rat study. There was no indication of teratological potential in a study with rabbits administered 150 mg/kg during organogenesis.

Acute toxicity of S-BA is low with all salt forms (acetate, carbonate, phosphate and hydrochloride) by several routes of administration. General sympathomimetic signs of acute poisoning have been noted in acute studies in rodents and dogs and in pharmacologic studies in dogs. Short and long term studies in rats and dogs suggest a no effect level (based on growth diminition) at 1250 ppm in rats (equivalent to 63 mg/kg/day) and 125 mg/kg/day in dogs. The value of 1250 ppm in rats is based on the effect on growth noted in the reproduction study (although this was not reflected in the two-year study).

Carcinogenic potential of S-BA appears to be low based on the rat feeding study. No specific mouse or other species was examined. Studies in man are not available although several letters attribute to the safety in use of S-BA to occupationally exposed individuals.

[A minor matter of concern might be the conversion of this primary amine to a nitroso derivative. This reaction is known to occur principally with secondary amine and nitrite. I believe this is not worth significant consideration.]

There are sufficient data to suggest an ADI although such studies as those for mutagenesis and such considerations as the occurrance of residues in milk and meat might reflect a temporary ADI be estimated with further work required in the area of concern - mutagenesis potential and reduction of residues. [Although rat pups are exposed to residues during the postnatal period and do not show any effects (except a slight reduction in growth in rats and in F2 of rabbits) I cannot personally pass off milk residues lightly. As milk makes up the sole diet of infants for several weeks at critical growth periods. I normally am over cautious with these considerations.]

Toxicological Evaluation

Level Causing No Toxicological Effect

Rat: 1250 ppm on the diet equivalent to 63 mg/kg body weight/day

Dog: 125 mg/kg/body weight/day

Estimate of Temporary Acceptable Daily Intake

0 - 0.6 mg/kg body weight

Further Work or Information

Required:

1. Studies on reduction of residues in meat and milk - time after feeding to reduce residues
2. Studies on mutagenic potential based both in vivo and in vitro techniques currently available.

ADDENDUM

This additional information is for use by members. This will not be part of the monograph.

Long Term Studies - Rat

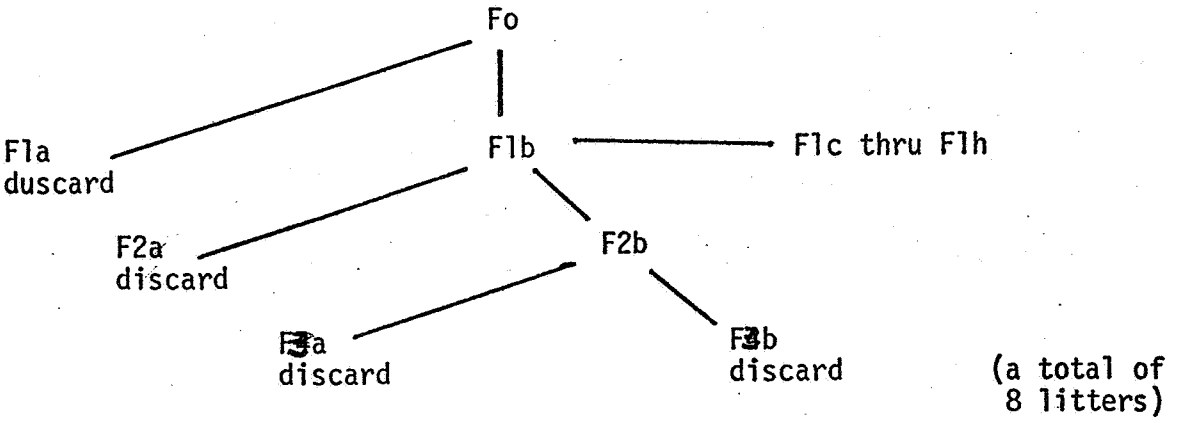
Groups of Harlan strain rats (30 males and 30 females per group) were fed Sec-butylamine acetate in the diet for 2 years at levels of 0, 1250, 2500 and 5000 ppm. Groups of rats (5 of each sex) were examined at 400, 428 and 449 days for possible reduction of WBC counts which had been noted in a 90-day study. At the conclusion of the study (732-733 days) all survivors were sacrificed. Clinical chemistry determinations were made on SGPT and blood glucose. In addition hematology measurements were made on: hemoglobin, RBC, lymphocytes, hematocrit and total and differential leukocytes. Growth curves are not reported but terminal weight averages show a reduction in males at 5000 ppm. Terminal weights are recorded for liver, kidney, heart, spleen, thyroid, adrenal, prostate and testes or ovary and uterus. In addition, microscopic examinations were made on lungs, thymus, mammary glands and on the presence of tissue masses. A finding of "light cell" ademona of the thyroid may be an artifact of the study the incidence of this occurrance is:

Dose	Sex	#ademona/#survivors	
0	M	1	9
	F	2	12
1250	M	4	8
	F	2	7
2500	M	2	13
	F	4	7
5000	M	6	13
	F	4	16

There were no records of the thyroid of animals not surviving for 2 years. However, this does not appear to be a significant occurrance. No data are presented on behavior or time of death during the study. A growth effect noted at 2500 ppm in the reproduction section is not reflected in these data. A no-effect level for this study would be 2500 ppm (Worth, et al 1969b).

Reproduction - Teratology

A standard 3 generation, 2 litter per generation reproduction study was modified as per the following design:



The reproductive capability of the original 3 groups of 20 males and 20 females was examined through 8 successive litters. At the last litter, the highest level fed had more dams than the low level. In the male mating efficiency, the treated males were more efficient over the whole study. An overall reduction in living fetuses was noted - 1% at 500 ppm and 2% at 2500 ppm - but was considered not significant.

The F1b, males and females were maintained on their respective dietary levels for 197 days before discarding; the F2b 162 (males) and 215 (females), days and the F3b 202 (males and females) days. The customary reproduction indices were recorded:

Fertility index = No. of matings resulting in pregnancy;

Gestation index = No. of young at birth;

Viability index = No. of young at 4 days;

Lactation index = No. of young at 21 days

At necropsy, gross and microscopic examination of tissues and organs included the following: heart, lungs, liver, spleen, thymus, kidney, G.I. tract, mammary gland, adrenal thyroid urogenital system and tissue masses.

Results of this study indicated no effect of Sec-butylamine on reproduction. A significant observation was the reduction in growth noted at 2500 ppm over the entire course of the experiment. This reduction was noted in all generations (Worth, et al, 1969).

A follow-up study of teratological findings was reported although it is difficult to evaluate the results. The results on p. G2 (5062-12-1199) indicate that only abnormalities are reported while many undescribed litters showed no abnormalities. However, the data on Table G1 (etc.) indicate (for example) sire number, dam number, mating trial, number of young examined and number of malformations. In no case do the number of young examined equal the malformations suggesting that only representatives were examined. This minor point might be resolved.

Results do not show a significant number of malformations or any special type in this study.

		No. Malformations	No. Examined
Fo	0	15	112
	500	19	24
	2500	22	136
F1	0	12	77
	500	12	72
	2500	6	65
F2	0	10	69
	500	14	83
	2500	8	67
F3	0	9	50
	500	5	40
	2500	11	53

The stained skeletons show no greater incidents of malformations than do the controls and no greater percentages of malformations over the four generations. No data are available on the additional litters from the Fo generation.

No significant teratological hazard was noted in this trial (Worth, et al, 1966).

Reproduction - Rabbit

Groups of dutch Belted rabbits were used for a reproduction study and in an effort to demonstrate the presence of Sec-butylamine in the milk. The initial protocol was for 3-dose levels of 0, 2500 and 5000 ppm

in the diet but, 5000 ppm proved to be detrimental to rabbits and the group was shifted to the lower level. In the two studies the following number of animals was used as parents:

Fo	Dose	F	M
	0	10	5
	2500	14	10
F1	0	8	5
	2500	12	6

Semen removed from treated males was used to inseminate the does. There was no difference in fertility as a result of this technique. The reproductive indices measured showed no differences from control values. The following is a summary of several parameters of the F1 and F2.

		No. Pregnant / No. bred	Births Live	Births still	Deaths 7 day	Deaths 56 day
F1	0	8/10	25	16	5	7
	2500	11/14	43	0	1	1
F2	0	5/8	27	11	9	14
	2500	11/12	51	7	8	9

Milk analyses, using a method reported to be sensitive to 0.01 ppm (p 5062-21-001) but showing only 72% recovery of pesticide from feed, were adequate to show the presence of Sec-butylamine at reasonably constant levels over the course of weaning. The pups were exposed to the pesticide in milk for their life time as they were exposed after weaning to dietary levels in a similar manner as their parents had been.

The growth of the F2 pups was slightly lower than the F1 and control values suggesting an effect of the toxicant. This cannot be fully evaluated as it was not evident in the 4 generation rat study.

The study shows that Sec-butylamine has no significant effect on reproduction although, again 2500 ppm is an effect level. The slight effect on growth of the F2 at 2500 ppm is suggestive of a marginal response (Gibson, et al 1970).

REFERENCES

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2-AMINOBUTANE

Bu^sNH_2

$C_4H_{11}N$ (73)

ZY2,

2-aminobutane, also known as sec.-butylamine, was introduced, in 1962, as a fungicidal fumigant by the University of California (Riverside) and was first so described by Eckert, J. W. and Kolbezen, M. J., *Nature, Lond.*, 1962, 194, 888. 'Tutane' is registered as a trade mark by Eli Lilly & Co.

It is a colourless liquid with an ammoniacal odour, b.p. 63°C; v.p. 135 mm. Hg at 20°C; n_D^{20} 1·394; d_4^{20} 0·724. It is miscible with water and most organic solvents.

It is an organic base forming water-soluble salts with acids. Having an asymmetric carbon, it exists as optical isomers. It is stable but corrosive to tin, aluminium and some steels.

2-aminobutane is a fungicide of promise for the control of many fruit-rotting fungi; aqueous solutions of its salts, containing 0·5 to 2% amine, are used as dips or sprays on harvested fruit to prevent decay in transport or storage. The amine may be used to fumigate harvested fruit at 100 ppm (v/v) for four hours, or its equivalent. In neutral aqueous solution, the hydrochlorides of the enantiomorphs show marked differences in fungicidal activity; the control of Penicillium decay of oranges is due largely to the *d* isomer: Eckert, J. W. and Kolbezen, M. J., *Phytopathology*, 1967, 57, 98. It is non-phytotoxic at ten times the recommended concentration.

The acute oral LD50 for rats is 380 mg amine/kg, for dogs 225 mg/kg, for hens 250 mg/kg. It is strongly irritant but the dermal toxicity for rabbits is more than 2,500 mg/kg. In two-year feeding tests, the 'no effect' level for rats and dogs is 2,500 ppm of the diet.

It is formulated as concentrated aqueous solutions of appropriate salts, preferably the acetate or phosphate.

Product analysis is by the steam distillation of the amine into standard acid and back titration. Residues may be determined by the steam distillation of the amine into dilute sulphuric acid which is neutralised, washed with carbon tetrachloride and reacted with 1-fluoro-2,4-dinitrobenzene in a borate buffer; the cyclohexane extract is then subjected to GLC: Day, E. W. *et al.*, *J. Ass. off. anal. Chem.*, 1968, 51, 39.