

UNDATED

MEMORANDUM

SUBJECT: ID. No. 283750, Metabolite (1-Butyl Isocyanate) from Aqueous Benlate

Tox. Chem. No.: 075A  
Bar Code #: D180269  
Record No. : S421093

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CONCLUSIONS:

Toxicology Branch I has no information on the metabolite, 1-butyl isocyanate (BIC) in the benomyl data base. Although this specific metabolite was not identified in the general metabolism studies, it is assumed that equimolar concentrations of BIC and MBC are produced upon cleavage of the parent compound and that the toxicity of the metabolite has been indirectly assessed. (See Discussion, below)

ACTION REQUESTED:

Comment on whether the metabolite identified in the Hawaii paper has been reported in the benomyl data base and its toxicological significance.

21

## DISCUSSION:

Based on the information available on the metabolism of benomyl in mammalian species, we can assume that the metabolite, BIC is formed by cleavage of the parent compound. This cleavage would be expected to result in equimolar concentrations of both MBC and BIC and by testing the parent, one has indirectly tested the metabolites. Additionally, if a comparison is made of the toxicity of benomyl and the toxicity of the metabolite MBC, one would find that the profiles of the two are very similar with regard to acute, subchronic and chronic toxicity and mutagenicity. This would indicate that the contribution of BIC to the overall toxicity of the parent compound in mammalian species is minimal. (See Table I for comparison of the tox. profiles of benomyl and MBC).

In mammalian species, it is possible that the BIC molecule is rapidly degraded, that its degradants are excreted and that BIC does not persist at detectable levels. On the other hand, as suggested by the paper from the University of Hawaii (Tang, et.al.), in aqueous solution, Benomyl breaks down to MBC and BIC, and under optimal conditions of increased availability of water and increased temperatures, the accumulation of BIC is also increased. The validity and the significance of these findings in non-mammalian systems should be addressed by product chemistry.

The toxic properties of the metabolite under these two scenarios may be different; therefore, it is advised that the Agency obtain additional data that will enable us to determine the potential human health hazards that may result from direct exposure to increased concentrations of BIC.

Based on the data that Tox Branch has reviewed for benomyl and MBC, we have concerns regarding the 1) inhalation toxicity of BIC and 2) the potential for BIC to cause dermal irritation and sensitization. Further comment on the toxicity of BIC will be reserved until Tox Branch has completed their evaluation of newly acquired data on this chemical.

<u>Study type/ Guideline #</u>	<u>Benomyl</u>	<u>Results</u>	<u>MBC</u>
83-3b mouse	dev NOEL 50 mg/kg LOEL 100 mg/kg (skel. abn.)		Species not tested
83-3b rabbit	Species not tested		dev NOEL 10 mg/kg dev LOEL = 20 mg/kg (decr litter size, incr # resorptions)
83-4 rat	NOEL 100 ppm LOEL = 500 ppm (decr. pup wts)		Study not conducted

\* This was a combined chronic/onco study.

#### MUTAGENICITY

Both chemicals were described as weak mutagens in mouse lymphoma studies. Benomyl was also positive for sister chromatid exchange and was mutagenic for *S. typhimurium* strains TA 1537 and 98.

#### OTHER TOX INFO

Both compounds were associated with decreased spermatogenesis. Neither compound was associated with delayed neurotoxicity in hens.

#### METABOLISM:

The major metabolites of benomyl in the urine are 5 hydroxy MBC. Comparative studies in mouse, rabbit and sheep revealed that the metabolite distribution in these three species was similar. The primary reactions involved in the metabolism of benomyl involve oxidation of the phenyl ring, followed by conjugation. Similar metabolites were found in studies conducted with MBC.

TABLE I  
TOXICITY PROFILES for BENOMYL and MBC

<u>Study type/ Guideline #</u>	<u>Benomyl</u>	<u>Results</u>	<u>MBC</u>
<b>ACUTES</b>			
81-1	LD50 > 5000 mg/kg		LD50 > 5000 mg/kg
81-2	LD50 > 2000 mg/kg		LD50 > 10,000 mg/kg
81-3	LC50 > 4.01 mg/L		LC50 > 5.9 mg/L
81-4	irritation to d 7		minimal irritation
81-5	mild irritation		no irritation
81-6	mild - mod. sensizr		no sensitization
<b>SUBCHRONIC</b>			
82-1a -rats	NOEL 500 ppm LOEL 2500 ppm based on incr. liver enzymes and wts		no study
82-1b -dogs	NOEL = 500 ppm LOEL 2500 ppm based on inc. SGPT, AP & A:G ratio		NOEL = 500 ppm LOEL 1500 ppm based inc. liver enz. and chngs in the liver & testes
<b>C-O-R-T</b>			
83-1a rat*	NOEL > 2500 no effect on sperm production		NOEL = 500 ppm LOEL = 5000, decr. RBC parameters
83-1b dog	NOEL = 500 ppm LOEL 2500 ppm (cirrhosis decr. body wts.		NOEL = 100 ppm LOEL 500 ppm liver path
83-2a rat*	Onco NOEL 2500 ppm Onco LOEL > 2500 ppm		Onco NOEL 10,000 ppm Onco LOEL > 10,000 ppm
83-2b mouse	Onco LOEL 500 ppm (liver neoplasia)		Onco LOEL < 500 ppm (liver carcinomas)
83-3a rat	dev NOEL = 30 mg/kg LOEL = 62.5mg/kg ( microphthalmia)		dev NOEL = 10 mg/kg LOEL = 20 mg/kg (skeletal efcts) at 90 mg/kg decr # of litters and decr. litter size, microphthalmia, hydrocephaly)