

PROJECT NO. BIL-61-5 METABOLIC
REPORT FILE BUTYL BENZYL PHTHALATE
(DOGS)

Industrial **BIO-TEST** *Laboratories, Inc.*

1810 FRONTAGE ROAD

NORTHBROOK, ILLINOIS

Telephone CRestwood 2-3030

REPORT TO

[REDACTED]

[REDACTED]

[REDACTED]

Metabolism of Butyl Benzyl Phthalate in Dogs

Introduction

A study was conducted in dogs to determine the general metabolic pathway of butyl benzyl phthalate. The primary objective of the investigation was to note similarities in phthalic acid excretion when compared to di-(2-ethylhexyl)-phthalate, an approved phthalate type ester plasticizer.

Procedure

[REDACTED] g
[REDACTED]
[REDACTED]
[REDACTED] stainless steel metabolism cages and total urine excreted was collected
[REDACTED].

On an absolute dosage basis the dogs received total doses of butyl benzyl phthalate of 52 grams (male) and 50 grams (female). The dogs had a moderate diarrhea for several days after dosing but no toxic symptoms were observed. The dogs were fed daily and water was offered ad libitum after dosing.

The urine was analyzed for phthalate according to the method of C. Shaffer, C. Carpenter and H. Smyth, Jr., Journal of Industrial Hygiene and Toxicology 27, 130 (1945).

Results and Discussion

The total urinary excretion of butyl benzyl phthalate was found to be

2.44% for the male dog and 5.56% for the female dog. These values are in line with urinary excretion values of 4.5% and 2.0% found for di-(2-ethylhexyl) phthalate. The minor differences are due to several factors such as dose, degree of absorption and the limitations of the analytical method.

The conclusion reached by Shaffer et. al., namely that the toxicity of the phthalate ester is largely or entirely due to the alcohol used in esterifying O-phthalic acid, is further supported by the results of this study.

The two alcohols in question are N-butyl alcohol and benzyl alcohol. It is well known that N-butyl alcohol is rapidly oxidized in animals.* Further, only a small amount (1.8%) is apparently available for direct conjugation with glucuronic acid and excreted in this form. It is logical to conclude that the butyl alcohol portion of butyl benzyl phthalate does not add significantly to the acute or chronic toxicity of this phthalate ester.

The other alcohol released by the hydrolysis of butyl benzyl phthalate in the body is benzyl alcohol. This substance has a reported LD₅₀ of 3.- g/kg in rats. It is a common component of perfumes, various drugs and food flavors. The invivo oxidation rate of benzyl alcohol is also

* H. Weese Arch. exp. Path. Pharmak., 135, 118 (1928) and S. Berggren Skand. Arch. Physiol. 78, 249 (1938)

very rapid and the benzoic acid formed (which has been safely used as a food preservative for many years) is excreted mainly (91-98%) as hippuric acid and partly as the benzoyl glucuronide.

On the basis of this brief study (which shows that the phthalate ester in question behaves metabolically as other phthalates approved as indirect food additives) plus a comprehensive 90-day toxicological study in rats and dogs (in which a treated control, butyl phthalyl butyl glycolate, was also included) it appears logical to conclude that butyl benzyl phthalate is safe and that the recommended manufacturing practices provide a high margin of safety.

The material in this report is to be used in development of the product and may be given to responsible sales contacts, but it is not to be used by them in advertising copy. The source of this material is not to be divulged until it appears in formal publications. No exceptions to the established rule may be made without the approval of the Medical Department in St. Louis. Customers' inquiries regarding matters of toxicity are to be referred as before to the Medical Department in St. Louis for reply.

— Monsanto Chemical Company

Rate of Excretion of Butyl Benzyl Phthalate in the Dog

Dog	Weight (kg)	Day	24-Hour Urine Volume (ml)	Excretion of Ester	
				Weight Excreted in 24-hrs. (grams)	Per Cent Total Dose
Male	9.6	1	410	1.1882	2.22
		2	300	0.0989	0.18
		3	<u>1000</u>	<u>0.0189</u>	<u>0.04</u>
		Total:	1710	1.3060	2.44
Female	10.0	1	172	0.4390	0.85
		2	263	1.5881	3.00
		3	<u>180</u>	<u>0.8900</u>	<u>1.71</u>
		Total:	615	2.8871	5.56

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

John H. Kay
 Report prepared by: John H. Kay, Ph.D.
 Associate Director

J. C. Calandra
 Report approved by: J. C. Calandra, M.D., Ph.D.
 Director

November 6, 1961