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Soil Adsorption Alters Bioavailability of Benzene in Dermally Exposed Male Rats

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The potential for exposure to chemically contaminated soil is a concern for chemical industry and waste disposal site workers individuals living near the contamination site. Current assessment of potential health risks from these types of exposures exclusively on extrapolations from data derived with pure chemicals. Complex interactions with soil, however, nuy alter gro which a chemical subsequently interacts with the body. This study was conducted to determine if soil adsorption alters the benzene, a common chemical contaminant, enters and is handled by the body following dermal exposure. A shallow glas approximately a 13-cm^2 area was fixed tightly to the shaved skin of each adult male rat tested; 300 μL of ^{14}C-benzene alone or or sandy soil was introduced under the cap tbrough an opening which was sealed immediately. Pure benzene produced the plasma concentration of radioactivity, followed closely by sandy soil–adsorbed benzene, with the lowest value exhibited by sorbed benzene. The plasma elimination half-lives were as follows: sandy (24.5 hr), pure (23.0 hr), and clay (19.4 hr). The tissue of radioactivity 48 hr post administration were highest in treated skin (covered by the glass up), followed by the kidney and soil-treated groups, and were highest in the kidney followed by the liver and treated skin in the pure group. A statistic radioactivity was observed in the treated skin of the clay versus pure group, while a statistical decrease was found in the treated skin covered by glass cap) in the same group. Forty-eight-hour studies revealed that radioactivity was excreted primarily in u lesser extent, in expired air and in feces for all groups. In all treatments, phenol was the primary metabolite with smaller hydroquinone, benzenetriol and catechol detected. These results show that differences in the bioavailability and tissue distributio occur following dermal exposure to soil-bound versus pure chemical, with the type of soil being an important factor. This info allow for a more precise estimate of potential health risk following exposure to chemically contaminated soils.

Introduction

Benzene is a common industrial chemical found in gasoline, solvents and starting materials for the synthesis of aromatic compounds.[1-3] Soil may become contaminated with benzene through hazardous waste disposal and through spills and leaks which may occur during manufacture, transport and storage. Employees may be exposed directly to contaminated soils at industrial facilities, while communities may be exposed indirectly via wind erosion, surface water runoff, or through projects that reuse the soil, *e.g.*, Love Canal.[3] Dermal contact with polluted soil is a potentially important exposure pathway in young children (ages 1.5–3.5). The U.S. Environmental Protection Agency (EPA), in its risk assessment analysis for children, based its estimates of dermal exposures to soil on actual field investigations. A study by Roels, *et al.* concluded that 0.5 mg of soil per cm^2 of soil may adhere to a child's hands after playing in and around the home.[4,5]

Until recently, evaluation of health risks associated with exposures to benzene have been based mainly on the results of inhalation studies conducted with the pure compound. Upon analyzing the detrimental effects of benzene on the working population, the National Institute for Occupational Health and Safety (NIOSH) recommended that the threshold limit value (TLV®) of benzene be reduced from 10 ppm to 1 ppm as determined by an air sample collect for 2 hr.[6,7]

Information on dermal exposure to benzene available. Franz[8] measured the percutaneous a benzene in animals and man. Following the appl thin layer of benzene (5–10 μL/cm^2) *in vivo*, a found to average less than 0.2% of the applied species studied. Susten, *et al.*[9] reported on a st less mice following the dermal application of a vent mixture containing 0.5% (v/v) benzene. their study, together with observations made d building operations, suggest that a worker could mg of benzene daily through the skin.

The physical and chemical parameters of particle size, percent organic content and perce ever, determine the degree to which pollutants to soil and, subsequently, the rate and amount which enters the body; its distribution to ti rate, amount and form which is eliminated Schlatter[10] conducted the first studies on the of soil-adsorbed chemicals. In their investiga dosed orally with laboratory prepared dibenzo-p-dioxin (TCDD) contaminated so availability was considerably lower after soil a after administration of an ethanolic solution was dependent on the duration of contact TCDD. Reduced dermal bioavailability of

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TABLE I
Soil Properties

	Cohansey	Woodbury
	90	58
	8	28
	2	22
matter (%)	4.4	1.6
size, mm (%)		
.1	22.2	17.0
.25	76.3	65.3
.5	1.2	13.6
.0	0.2	3.4
.0	0.1	0.7
	0	0.1

was observed by the same group. Lucier, *et al.*[11] ell, *et al.*[12] suggest that TCDD contaminated e Minker Stout and Times Beach sites in present a health hazard if ingested because of high toxicity and relatively high bioavailabil- clusions were based on microsomal enzyme TCDD liver concentrations in guinea pigs trary to the Missouri soil studies, Umbreit, allo[13] demonstrated that despite its high , soil from a Newark, New Jersey, manufac- not induce acute toxicity in guinea pigs. ver samples showed low bioavailability of he New Jersey soil. The differences in bio- tween the soils can be correlated with differ- mposition of the soils.

ors' laboratory, statistically significant differ- erved in plasma kinetics and excretion follow- nistration of benzene adsorbed to two New Dermal contact represents an additional exposure to benzene-contaminated soil parti- y was performed to assess differences in bio- soil-adsorbed versus pure forms of benzene in ollowing dermal administration.

d Methods

icals and Soils

-Dawley rats, weighing 275–300 g, were pur- Taconic Farms, Germantown, New York and quarantined for 1 week. The rats were main- cage in a temperature (25 °C) and humidity rolled environment with a 12-hr light/dark cycle. chow (Ralston Purina, St. Louis, Mo.) and provided *ad libitum* before and during the

ne with a specific activity of ical purity of ≥ 98% was ceuticals, Irvine, California. ted with nonradioactive, Chemical Co., Milwaukee, ock solution of 133.3 mCi/mL.

Two soils were utilized: (1) an Atsion soil collected from an outcrop site of the Cohansey sand formation near Chatsworth in southcentral New Jersey and (2) a Keyport soil collected from the Woodbury formation near Moorestown in southwestern New Jersey. The Atsion is a deep, poorly drained soil formed (> 150 000 acres) in Atlantic coastal plain sediments of New Jersey and New York. Warmer thermic equivalent Leon soil is found extensively (>500 000 acres) in Maryland, Virginia, North Carolina, South Carolina, Alabama, Georgia and Florida.[15] The Keyport is a moderately well drained soil formed on clay bed marine deposits of the Atlantic inner-coast plain. Moderate amounts (>70 000 acres) of Keyport soil are found in New Jersey, Delaware, Maryland and Virginia with similar soils occurring from New Jersey to Texas.[''''

Mechanical, sieve and organic matter analyses were performed (Table I) by the Cooperative Extension Service, Cook College, Rutgers University, New Brunswick, New Jersey. Physical characteristics of the soils are summarized in Table I. Contamination by benzene, toluene or chlorinated hydrocarbons was determined on combined ether-hexane (1:1) and methylene chloride soil extracts. Gas chromatography/mass spectrometry (Hewlett Packard model 5995A) analysis of the extracts using OV-17 and Tenax columns (Supelco, Bellefonte, Pa.) and by direct probe did not detect these contaminants.

Absorption and Elimination Studies

One-half hour prior to the dermal application of benzene, three groups of five rats were shaved on their right costo-abdominal areas. A shallow glass cap (Q Glass Company, Towaca, N.J.), circumscribing approximately a 13-cm^2 area was tightly fixed with Lang's jet liquid acrylic and powder (Lang Dental Manufacturing Company, Inc., Chicago, Ill.) on the shaved skin of each animal. Rats were anesthetized with ether during the cap attachment procedure. Either 300 μL of stock ''C-benzene (40 μCi) alone or with 1 g of soil was introduced by syringe through an opening in the cap which was immediately sealed. This volume of benzene coated the soil with no excess fluid remaining. Radioactivity was mea-

TABLE II
Absorption and Elimination Half-Lives of Radioactivity in Male Rat Plasma[A]

	$t_{1/2}$ (hr)	
Treatment	Absorption	Elimination
Benzene[B]	3.1	23.0
Sandy[C]	3.6	24.5
Clay[D]	4.4	19.4

[A] Values represent six male rats per group following the dermal administration of ^{14}C-Benzene alone or adsorbed to soil.
[B] ^{14}C-Benzene alone
[C] ^{14}C-Benzene adsorbed to sandy *soil*
[D] ^{14}C-Benzene adsorbed to clay soil

surable in plasma only when a minimum of 40 μCi of ^{14}C-benzene was administered topically. The animals were rotated from side to side so that the soil-chemical mixture covered the entire circumscribed area. Heparinized blood samples were collected by cardiac puncture under light ether anesthesia at 2, 4, 8, 12, 24, 30, 48 and 72 hr. Samples were processed and radioactivity was measured by liquid scintillation spectrometry as previously reported.''''

Excretion, Distribution and Metabolism Studies

Urine, feces and expired air were collected and analyzed by established techniques.'''' At the conclusion of the excretion studies, rats were sacrificed by an overdose of ether. The glass caps were opened, and 1.0 to 1.2 mL of ethyl alcohol was introduced through the cap opening. The animals were rotated from side to side, and 100 μL aliquots of ethanol wash were removed to scintillation counting vials containing 10 mL of Aquasol-2 to determine the percent of benzene dose remaining on the skin application sites. Then, the glass caps were removed from the rats and tissue specimens were collected. Radioactivity was determined as previously described.[14]

Ethyl acetate-extracted urine samples were analyzed by high performance liquid chromatography under the same conditions used in previous oral benzene studies.'''' The efficiency of extraction was greater than 95%.

Data Analysis

Exploratory data analyses were utilized to summarize replicate data in the plasma time course study. This approach allows a curve to be fitted to all data points while providing resistance to those points which depart from the primary pattern.[17,18] The curve-fitting procedure which was utilized is called smoothing. For these studies a "4235EH" smoother (a statistical procedure for treating the data) was used.[18] Each replicate was smoothed over all time points, a median value was calculated from all smooth replicates at each time point, and a second smooth was applied to these median values. This final smoothed data was used to calculate the rate constants and $t_{1/2}$ of absorption and elimination from plasma by regression analysis and the method of residuals[19] as well as to determine a maximum concentration and a time at which the maximum concentration was achieved. Plasma concentrations from 0 min to the time at which maximum concentration was achieved were used for absorption calculations, and those for 12 through 72 hr and 24 through 72 hr were used for elimination calculations in the soil and pure groups, respectively. Since the rate constants and $t_{1/2}$s were calculated from smoothed data, the standard errors (SE) of the rate constants were determined by the bootstrap method.[20,21] The area under the plasma-time curve (AUC) was calculated by the trapezoidal rule using individual replicate data, does reflect volatilization losses, and is reported as the mean ± standard error of the mean (SEM). All other data are reported as mean ± SEM. Statistical differences between the treatment groups were determined by analysis of variance (ANOVA), F test, and Scheffe's multiple range rest; and comparisons of slopes were determined using analysis of covariance. All calculations included corrections for volatilization losses of 67%, 59% and

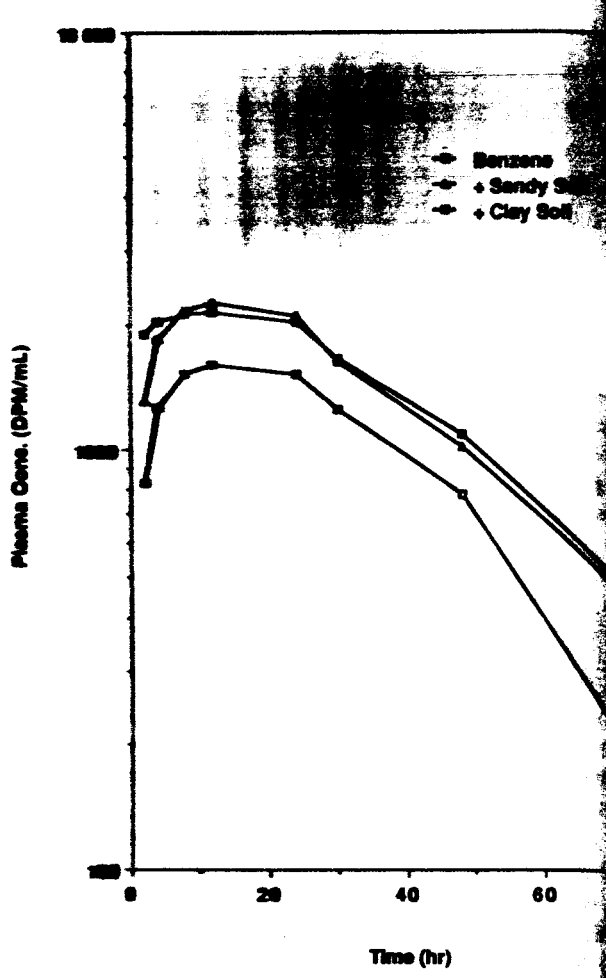

Figure 1—Plasma concentration of radioactivity in [illegible] following dermal administration of ^{14}C-benzene. M[illegible] were treated dermally with 300 μL benzene (40 μCi) [illegible] without 1 g of soil. At 2, 4, 8, 12, 24, 30, 48 and 72 hr, all [illegible] blood were collected by cardiac puncture and plas[illegible] assayed for radioactivity. Values represent the final sm[illegible] data for N = 5 per treatment.

39% of radioactivity, respectively, during the admini[illegible] of ^{14}C-benzene alone or in the presence of sandy or cl[illegible]

Results

The absorption and elimination plasma time courses f[illegible] activity associated with dermally administered ^{14}C-[illegible] alone or adsorbed to sandy or clay soil are shown in [illegible] Clay soil-adsorbed benzene produced a statistic[illegible] peak plasma concentration of radioactivity (1606 [illegible] tions per min [DPM]/mL). Peak ^{14}C plasma lev[illegible] and 2262 DPM/mL were reached 12 hr after adm[illegible] of ^{14}C-benzene and sandy soil-adsorbed benzene, [illegible] Neither of the soils changed the time to reach peak [illegible] tions compared to pure benzene. Both soils, howe[illegible] cantly decreased ($p < 0.001$) area under the plasm[illegible] (AUC) values (0.22 ± 0.08, 0.17 ± 0.07, and 0.41 ± 0[illegible] dose/mL·hr, respectively, for sandy soil, clay soil [illegible] alone). The absorption half-lives [illegible] for pure, sandy and clay soil-adsorbed benzene, [illegible]

III). The presence of sandy soil increased the elimination [illegible] clay soil decreased the elimination [illegible] compared to pure benzene (23.0 hr). No statistically significant differences were determined, however, in either the absorption or elimination [illegible] between groups.

In all treatment groups, the major route of excretion was the urine and, to a lesser extent, the expired air (Table III). The highest amount of radioactivity in urine appeared in the 0–12 hr interval (58.8%, 31.3% and 25.1% of the initial dose, respectively, for pure, sandy and clay soil–adsorbed benzene). During the 48-hr collection period, 86.2% of the initial dose was excreted in the urine of the pure benzene group. Sandy soil and clay soil significantly decreased urinary excretion to 64.0% and 45.4%, respectively, of the initial dose during the same time period. The major portion of radioactivity in expired air was exhaled as the parent compound in the first 12 hr (Table III). Rats receiving pure benzene excreted 12.8% of the initial dose in expired air within 48 hr. The percentage of radioactivity in expired air of the sandy groups was significantly lower than the other groups. Only 5.9% of the radioactivity was collected in expired air 48 hr after treatment with sandy soil–adsorbed benzene, while experiments with clay soil–adsorbed benzene revealed that 10.1% of the radioactivity was located in expired air. Less than 1% of the administered dose was expired as $^{14}CO_2$ in all groups. The ^{14}C activity in the feces was small (< 0.5%) in all groups during the 48-hr collection period.

Soil-related differences were found in tissue distribution following treatment. The distribution patterns of ^{14}C activity for pure and soil-adsorbed benzene are presented in Table IV. The ^{14}C activity 48-hr post-administration of soil-adsorbed benzene was greatest in the treated skin followed by the kidney and liver in both soil groups. In the pure benzene group, the kidney contained the largest amount of radioactivity followed by liver and treated skin. Clay soil treatment statistically increased radioactivity (10-fold) in treated skin while statistically decreasing radioactivity (4–fold) in treated fat compared to benzene alone. Ethanol extraction studies at necropsy revealed that only 0.1% of the initial dose was retained loosely on the application sites of all groups.

Phenol was the major urinary metabolite detected in the 0–12 hr urines of all treated groups (Table V). Smaller quantities of hydroquinone, catechol and benzenetriol were detected also. Similar metabolite percentages were detected in 12–24 and 24–48 hr urines of all treated groups (data not shown). Hydroquinone was decreased statistically in the 0–12 hr interval of the sandy treatment group. Use of acid hydrolysis in the preparation of urinary extracts did not permit identification of conjugation products.

Discussion

The data presented in this paper demonstrated that soil decreased the bioavailability of benzene when male rats were treated topically with benzene adsorbed to either a sandy or a clay soil. The relatively stronger adsorbance of benzene to clay soil is supported by a sustained lower plasma concentration and a significantly decreased AUC. Also, radioactivity was statistically lower in the fat and statistically higher in the skin application sites of the clay-soil treated animals. Both soil groups showed a significantly lower amount of ^{14}C activity in urine compared to the pure group, while radioactivity in expired air was decreased mainly after sandy soil administration.

The greater affinity of benzene for the clay soil in this investigation correlates with the results of the authors' previous oral, soil–adsorbed benzene study in male rats.[14] Dermal exposure of pure and soil-adsorbed benzene reached plasma concentrations of radioactive compound comparable to those generated by oral administration, however, only when rats were exposed to 8 times the concentration of ^{14}C-benzene (40 μCi). Peak plasma concentrations produced by dermal treatments were delayed approximately 36-fold (12 hr) compared with those which occurred following oral exposure (20 min). In addition, the half-lives of ^{14}C-benzene elimination from the plasma of all dermally exposed groups were considerably longer (20-fold) than those seen following oral administration of benzene. The percentage and time of

TABLE III
Excretion of Radioactivity in the Male Rat[A]

Time (hr)	Urine			Feces			Expired Air		
	Benzene[B]	Sandy[C]	Clay[D]	Benzene	Sandy	Clay	Benzene	Sandy	Clay
0–12	9.7 ± 3.8	16.2 ± 0.1	7.2 ± 1.7				9.4 ± 1.0	3.9 ± 0.8[E]	8.5 ± 1.2
12–24	58.8 ± 2.8	31.3 ± 2.8'	25.1 ± 3.4'				2.5 ± 0.4	0.4 ± 0.1'	1.1 ± 0.2'
0–24	68.4 ± 2.9	47.4 ± 2.2[E]	32.3 ± 4.0'	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	12.0 ± 1.4	4.3 ± 0.8[E]	9.6 ± 1.3
24–48	17.8 ± 1.8	16.6 ± 1.1	13 1 ± 1.9	0 1 ± 0.0	0 1 ± 0.0	0.1 ± 0.0	0.8 ± 0.2	1.6 ± 0.5	0.5 ± 0.2
0–48	86.2 ± 2.1	64.0 ± 2.8[E]	45 4 ± 4.8[E]	0.2 ± 0.1	0 1 ± 0.0	0.2 ± 0.0	12.8 ± 1 1	5.9 ± 1.3'	10.1 ± 1.4

[A] Values represent percentage initial dose (mean ± S.E.M.) of 3 groups (2 rats per group) treated dermally with ^{14}C-benzene alone or adsorbed to soil

[B] ^{14}C-Benzene alone

[C] ^{14}C-Benzene adsorbed to sandy soil

[D] ^{14}C-Benzene adsorbed to clay soil

[E] Significantly different from treatment with benzene alone ($p < 0.05$)

TABLE IV

Tissue Distribution of Radioactivity in the Male Rat[A]

Tissue	Percent of Initial Dose/Gram Tissue[B]		
	Benzene[E]	Sandy[F]	Clay[G]
Kidney	0.026 ± 0.001	0.024 ± 0.004	[illegible]
Liver	0.013 ± 0.002	0.013 ± 0.002	[illegible]
Treated skin[I]	0.011 ± 0.004	0.059 ± 0.027	0.119 ± 0.035[J]
Duodenum	0.010 ± 0.002	0.010 ± 0.001	0.005 ± 0.001
Treated fat[I]	0.008 ± 0.002	0.006 ± 0.001	0.002 ± 0.000[J]
Untreated fat[G]	0.005 ± 0.002	0.004 ± 0.000	—*a—
Bone marrow	0.005 ± 0.000	0.003 ± 0.001	0.003 ± 0.000
Gut fat	0.003 ± 0.000	0.004 ± 0.000	0.003 ± 0.000
Esophagus	0.003 ± 0.000	0.003 ± 0.001	0.002 ± 0.000
Pancreas	0.003 ± 0.000	0.002 ± 0.000	0.002 ± 0.000
Lung	0.003 ± 0.000	0.003 ± 0.000	0.002 ± 0.000
Heart	0.003 ± 0.000	0.003 ± 0.000	0.002 ± 0.000
Spleen	0.003 ± 0.000	0.007 ± 0.000	0.003 ± 0.000
Whole blood[H]	0.004 ± 0.000	0.004 ± 0.000	0.003 ± 0.000
Brain	0.002 ± 0.000	0.001 ± 0.000	0.001 ± 0.000
Thymus	0.002 ± 0.000	0.002 ± 0.000	0.001 ± 0.000
Thyroid	0.001 ± 0.000	0.002 ± 0.000	0.002 ± 0.001
Adrenal	0.003 ± 0.001	0.003 ± 0.001	0.001 ± 0.000
Testes	0.001 ± 0.000	0.001 ± 0.000	0.001 ± 0.000
Untreated skin	0.002 ± 0.000	0.003 ± 0.000	0.002 ±
Carcass	0.002 ± 0.000	0.001 ± 0.000	0.001 ± 0.000

[A] Values represent the mean ± S.E. for 5 male rats per group, 48 hr following the dermal administration of ^{14}C-benzene alone or adsorbed to soil.

[B] ^{14}C-Benzene alone

[C] ^{14}C-Benzene adsorbed to sandy soil

[D] ^{14}C-Benzene adsorbed to clay soil

[E] Area treated with benzene and covered with glass cap

[F] Fat beneath treated skin

[G] Fat beneath untreated skin (on side of rat opposite that of treated skin)

[H] Reported as percent initial dose/mL

[I] Significantly different from treatment with benzene alone ($p < 0.05$)

appearance of excreted benzene metabolites in the dermal study are in agreement with the authors' oral, soil-adsorbed benzene results.

In this study, recovery of the pure benzene compound was greater than 90%. Franz[23] and Susten, *et al.*[25] reported percutaneous absorption of benzene as 0.2% and less than 1%, respectively. Franz applied ^{14}C-benzene to the backs of the animals and allowed the chemical to flow over the skin seeking its own area. Under the conditions of Franz's experiments, the material quickly volatilized and was lost to the atmosphere. The current research incorporated a glass cap arrangement, while Susten, *et al.* used a skin depot to minimize volatilization losses of benzene. Further, Susten, *et al.*[25] conducted their experiments for 4 hr, while the present studies were extended to 72 hr. The principal conditions which affect dermal absorption of a compound are concentration and degree of lipid solubility of the chemical, time and site of skin exposure, peripheral blood flow, body temperature, and skin disease or injury.[23] Soil contact was a major factor in increasing percutaneous absorption in the present investigation.

The two most important components of soil affecting toxicant persistence are organic matter and clay content of the soil.[23] In both dermal, and oral, soil-adsorbed benzene studies, results indicated that a higher percentage of clay rather than organic matter was governing the bioavailability of benzene in soil and, therefore, altering the bioavailability of benzene to the male rat. These results suggest that the potential risks from dermal exposure to a high level of clay-adsorbed benzene (300 μL/g soil) are less than those from oral exposure to the pure or sandy soil-adsorbed benzene.

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References

1. **Bassit**, R.C.: *Disposition of Toxic Drugs and Chemicals in Man*. 2nd ed. Davis, Calif.: Biomedical Publications, pp. 71–75.
2. **Sandmeyer, E.E.**: Aromatic Hydrocarbons. In *Industrial Hygiene and Toxicology*, edited by G. F.E. Clayton. Vol. 2B. New York: John Wiley & Sons, pp. 3253–3432.
3. **Ross, S.S.**: Toxic Substances: A Review. In *Toxic Source* Book, Series 2, edited by R. Mogilan. Environmental Information Center, Toxic Substance Dept., 1980, pp. 15–20.

TABLE V

Urinary Metabolites of ^{14}C-Benzene in the Male Rat[A]

Metabolite	Treatment	
	Benzene[B]	Sandy[C]
Phenol	37.7 ± 3.1[E]	44.2 ± 4.3
Catechol	13.1 ± 1.1	14.4 ± 4.9
Hydroquinone	19.0 ± 1.6	10.2 ± 1.3
Benzenetriol	5.4 ± 2.2	17.3 ± 6.8

[A] Three groups (2 rats per group) treated [illegible]

[B] ^{14}C-benzene alone or adsorbed to soil

[C] ^{14}C-Benzene alone

[D] ^{14}C-Benzene adsorbed to [illegible]

[E] Values represent percentage [illegible] ± S.E.M. in 0-12 hr [illegible]

[illegible]

[illegible] Exposure to Lead [illegible]

[illegible] Murray: A Critical [illegible] Risk Assessments of [illegible] Pharmacol. [illegible]

[illegible] Solvents and Chemical Intermediates. In *Hand-[illegible]ology*, edited by T.J. Haley and W.O. Berndt. [illegible] Publishing Corporation, 1987. pp. [illegible]

[illegible] Institute for Occupational Safety and Health: [illegible] *Recommendation for an Occupational [illegible] Standard for Benzene.* Cincinnati, Ohio: U.S. [illegible] of Health, Education and Welfare, Public Health [illegible] Center for Disease Control, 1976.

[illegible] Percutaneous Absorption of Benzene. In *Advances [illegible] Environmental Toxicology, Applied Toxicology of [illegible] Hydrocarbons*, edited by H.N. MacFarland, C.E. [illegible]worth, J.A. MacGregor, R.W. Cali and M.L. Lane. Vol. [illegible]nceton, N.J.: Princeton scientific Publishers, Inc.. [illegible] pp. 61-70.

[illegible], A.S., B.L. Dames, J.R. Burg and R.W. N——— [illegible]aneous Penetration of Benzene in Hairless Mice: An [illegible] of Dermal Absorption during Tire-Building Opera- [illegible] *Am. J. Ind. Med.* 7:323-335 (1985).

[illegible], H. and C.H. Schlatter: Influence of Solvents and [illegible]nts on Dermal and Intestinal Absorption of TCDD. [illegible] *Toxicol.* 18:477-481 (1980).

[illegible] G.W., R.C. Rumbaugh, Z. McCoy, R. Hass, D. [illegible] and P. Albro: Ingestion of Soil Contaminated with [illegible]trachloro-dibenzo-p-dioxin (TCDD) Alters Hepatic [illegible] Activities in Rats. *Fundam. Appl. Toxicol.* 6:364-[illegible]).

12. McConnell, E.E., G.W. Lucier, R.C. Rumbaugh, P.W. Albro, [illegible] in Soil [illegible]

13. [illegible] T.H., E.J. Hesse and M.A. Gallo: Bioavailability of Dioxin in Soil from a 2,4,5-T Manufacturing Site. *Science* [illegible] (1985).

14. Turkall, R.M., G. Skowronski, S. Gorges, S. Von Hagen and M.S. Abdel-Rahman: Soil Adsorption Alters Kinetics and Bioavailability of Benzene in Orally Exposed Male Rats. *Arch. Environ. Contam. Toxicol.* 17:159-164 (1988).

15. National Cooperative Soil Survey: *Official Series Description-Atsion Series.* Washington, D.C.: United States Department of Agriculture—Soil Conservation Service, 1977.

16. National Cooperative Soil Survey: *Official Series Description—Keyport Series.* Washington, D.C.: United States Department of Agriculture—Soil Conservation Service, 1972.

17. Tukey, J.W.: *Exploratory Data Analysis.* Reading, Mass.: Addison Wesley, 1977. pp. 205-235.

18. Velleman, P.F. and D.C. Hoaglin: *Applications, Basics and Computing of Exploratory Data Analysis (ABC's of EDA).* Boston, Mass.: Duxbury Press, 1981. pp. 159-200.

19. Gibaldi, Y. and D. Perrier: *Pharmacokinetics.* New York: Marcel Dekker, 1975. pp. 281-292.

20. Efron, B.: *The Jackknife, the Bootstrap and Other Resampling Plans.* Philadelphia, Pa.: Society for Industrial Applied Math, 1982.

21. Efron, B. and R. Tibshirani: *The Bootstrap Method for Assessing Statistical Accuracy* (Technical Report 101). Stanford, Calif.: Division of Biostatistics, 1985.

22. Malkinson, F.D. and L. Gehlmann: Factors Affecting Cutaneous Toxicity. In *Cutaneous* Toxicity, edited by V.A. Drill and P. Lazark. New York: Academic Press, Inc., 1977. pp. 63-81.

23. Duffus, J.H.: *Environmental Toxicology.* New York: John Wiley and Sons, 1980. pp. 101-102.

31 August 1967; Revised 6 May 1988