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DERMAL ABSORPTION OF CHEMICALS: EFFECT OF APPLICATION OF CHEMICALS AS A SOLID, AQUEOUS PASTE, SUSPENSION, OR IN VOLATILE VEHICLE

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The purpose of this study was to investigate the dermal absorption of chemicals in different physical forms when applied to female F344 rats. Chemicals were applied either as a solid, aqueous paste, suspension, or dissolved in the volatile vehicle ethanol. The chemicals investigated were [^{14}C]-2-sec-butyl-4,6-dinitrophenol (DNBP, 4.2 μmol), 2,4,5,2',4',5'-[^{14}C]-hexachlorobiphenyl (HCB, 2.3 μmol), and 3,4,3',4'-[^{14}C]-tetrachlorobiphenyl (TCB, 0.5 pmol). The chemicals were applied on the clipped mid-dorsal region of the rat over a 2.54-cm^2 treatment area, which was then occluded. Urine and feces were collected and assayed for radioactivity. Twenty-four hours post-application, the treated skin was washed with a mixture (1:1) of soap and water, dried, and reoccluded. The animals were sacrificed at 120 h by exsanguination under ether anesthesia. Radioactivity in the blood, skin (treated and untreated), and carcass was assayed. Dermal absorption of DNBP-derived radioactivity was approximately 50% of the recovered dose after application in the four physical forms, and the major route of excretion was via the urine. Twelve percent of the absorbed dose of DNBP was retained in the body. Dermal penetration of HCB-derived radioactivity was 5–8% of the recovered dose after application in the four forms, and the major route of excretion was via the feces. Greater than 90% of the absorbed dose of HCB-derived radioactivity was retained in the body. Dermal penetration of TCB-derived radioactivity was 6–8% of the recovered dose in the four forms, and the major route of excretion was via the feces. Approximately 21% of the absorbed dose was retained in the body at 120 h.

The research described in this article has been reviewed by the Health Effects Research Laboratory, U.S. Environmental Protection Agency, and approved for publication. Approval does not Signify that the contents necessarily reflect the views and policies of the agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

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Absorption of each chemical applied either as solid, aqueous paste, or suspension was compared to the absorption of the same chemical in ethanol. Absorption of HCB applied as a solid was significantly higher ($p \leq .05$) as compared to HCB applied in ethanol. There were no other significant differences in the comparisons of absorption. The data indicate that the chemicals examined in this study can penetrate the skin as readily when applied either as a solid, aqueous paste, or suspension, as when applied in the volatile vehicle ethanol.

INTRODUCTION

An important toxicological aspect in occupational and environmental settings is the dermal exposure to chemicals and the potential for their penetration and elicitation of systemic toxic effects (Birmingham, 1976). Skin provides a barrier to the absorption of many chemicals, but penetration through this viable and heterogeneous organ can occur (reviewed by Scheuplein and Blank, 1971). Many factors have been experimentally shown to influence dermal penetration of chemicals. Some of these factors include species (Moody and Franklin, 1987; Moody et al., 1987; Sidon et al., 19881, age (Banks et al., 1990; Shah et al., 1987), site of application (Maibach et al., 1971; Wester et al., 1980), hydration state of the skin (Blank, 1985; Idson, 19781, and physicochemical properties of the vehicle used to apply the chemical onto the skin (Barry, 1983; Idson, 1983).

Dermal exposure to chemicals in solid form may occur in many environments, such as during the application of pesticides in dust formulation to crops (Wolfe et al., 1967) or working with soil treated with polychlorinated biphenyl-contaminated dried sludge (Bergh and Peoples, 1977). The development of risk assessment for absorption of chemicals after this type of exposure is difficult, because of the limited experimental data on the dermal absorption of chemicals applied directly to skin in solid form. One method to apply or "deposit" chemicals in solid form is to use small volumes of highly volatile organic solvents (Feldman and Maibach, 1970; Scheuplein and Ross, 1974). The solvents are used to dissolve the chemicals and achieve uniform dosing onto the skin. After the solvent volatilizes, it is believed that a microcrystalline layer of the chemical is left on top of the skin. Chemicals applied by this method are able to penetrate the skin and enter the systemic circulation. However, it is not known how absorption of chemicals applied by this method differs from that of chemicals applied directly as a solid.

Many physical tasks result in enhanced perspiration, which may increase the hydration of skin. The hydration state of the skin has a significant effect on the penetration of chemicals (Blank, 1985; Idson, 1978). Experimentally enhanced hydration of skin increases the rate of diffusion of chemicals (Cronin and Stoughton, 1962; Fritz and Stoughton, 1963; McKenzie, 1962). In humans, penetration of chemicals is enhanced under conditions of elevate might propose that cont may result in increased a of dermal absorption of to be important.

The objective of this of chemicals applied in d cals included solid, aque tile vehicle ethanol. Th dinitrophenol (DNBP), 3,4,3′,4′-tetrachlorobiph model compounds prim tanol :water partition coe solubilities are 100 ppm c as a solid, aqueous past absorption of the same c

MATERIALS AND ME

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der conditions of elevated humidity and temperature (Idson, 1978). One might propose that contact of a chemical in solid form to hydrated skin may result in increased absorption of the chemical. Thus, investigations of dermal absorption of chemicals applied in solid form are considered to be important.

The objective of this study was to investigate the dermal absorption of chemicals applied in different physical forms. The forms of the chemicals included solid, aqueous paste, suspension, or dissolved in the volatile vehicle ethanol. The chemicals investigated were 2-*sec*-butyl-4,6-dinitrophenol (DNBP), 2,4,5,2′,4′,5′-hexachlorobiphenyl (HCB), and 3,4,3′,4′-tetrachlorobiphenyl (TCB). These chemicals were chosen as model compounds primarily for their low water solubility. Their octanol:water partition coefficients (log *P*) vary almost fourfold, and water solubilities are 100 ppm or less. The absorption of each chemical applied as a solid, aqueous paste, and suspension was then compared to the absorption of the same chemical applied in the volatile vehicle ethanol.

MATERIALS AND METHODS

Uniformly [^{14}C]-ring-labeled DNBP (specific activity 4.29 mCi/mmol) was purchased from Chemsyn Science Laboratories (Lenexa, Kans.). DNBP has a log *P* of 3.7 and water solubility of 100 ppm. Uniformly [^{14}C]-ring-labeled TCB (37.1 mCi/mmol) and HCB (17.6 mCi/mmol) were purchased from Sigma Chemical Co. (St. Louis, Mo.). TCB and HCB have log *P* of 6.5 and 7.4 and water solubilities of 175 and 1.3 ppb, respectively. The manufacturers' reported radiochemical purity of each chemical was greater than 98%.

Female Fischer 344 rats were purchased from Charles River Laboratories (Raleigh, N.C.). The animals were initially housed in the animal facility on a 12-h light/dark cycle at constant temperature (22 ± 2°C) and humidity (50 ± 10%) and provided with food (Purina Rat Chow, St. Louis, Mo.) and tap water ad libitum.

The experimental protocol described by Shah et al. (1987) was followed with some modifications. The animals (90 d old, 156–175 g) were lightly anesthetized with ethyl ether and hair on the backs was removed with electric clippers (size 40, Oster Corp., Milwaukee, Wis.) 24 h prior to treatment. The clipped area was washed with acetone to remove dirt and sebaceous gland secretions. The animals were placed in individual Nalgene metabolism cages (Nalge *Co.*, Rochester, N.Y.) for overnight acclimation and provided with Dustless Precision Pellets (Bioscience, Inc., Frenchtown, N.J.) and water ad libitum. The following day, the animals were lightly anesthetized with ether and a circular area of 2.54 cm^2 was marked in the clipped mid-back with a pen and template. The selected chemical was applied within the marked area of each animal in one of four physical forms. These forms included the chemical dissolved in the

volatile vehicle ethanol, as a solid, aqueous paste, or suspension. In the case of the application with volatile vehicle, the dissolved chemical was applied (25 μl) as individual droplets from a Hamilton microliter syringe (Reno, Nev.) so as to dose the entire marked skin surface area. An applicator was designed to apply the chemical in solid form and consisted of a Teflon disc (1.13 cm^2) glued to the large open end of a 1-ml plastic pipette tip. The chemical dissolved in ethanol (25 μl) was applied in individual droplets (approximately 2–5 μl) to cover the disc and the ethanol was allowed to evaporate. The applicator disc with dried chemical was then rubbed carefully against the skin within the entire marked area. This procedure lasted less than 5 s and did not appear to cause any irritation or damage to the skin. One applicator was used for each animal. In the cases of the chemical applied as an aqueous paste or suspension, 10 and 50 μl of water, respectively, was applied to the skin within the marked area. An applicator disc with the chemical in solid form (see above) was then immediately rubbed onto the hydrated skin, forming an aqueous paste or suspension. Four animals were used per chemical per physical form. The amount of the chemical applied to the skin or placed on the applicator dissolved in ethanol was 4.2 pmol for DNBP, 2.3 pmol for HCB, and 0.5 pmol for TCB. Radioactivity remaining on the disc after rubbing it on the skin was determined by placing it in a vial with scintillant and counting it in a scintillation counter (described later). The mean transfer from disc to skin of the chemicals in the various forms ranged from 78 to 90% for DNBP, 78 to 82% for HCB, and 94 to 97% for TCB. The amount of the chemical transferred to the skin from the applicator was considered to be the applied dose. The treated area was covered and occluded by gluing a plastic blister (Millipore Corp., Bedford, Mass.) on the animals with a cyanoacrylate adhesive (Locite Corp., Newington, Conn.). The animals were restrained from damaging the protective blister by securing a collar of latex tubing with 20-gauge bus wire behind the forelegs as described by Bartek et al. (1972). The treated animals were housed for 120 h in the metabolism cages for collection of urine and feces.

Twenty-four hours postapplication, each animal was lightly anesthetized with ether, the top of the plastic blister was cut open, and the treated skin was washed three times with a 1-ml mixture (1:1) of soap (Ivory) and water using a cotton ball and forceps. The area was then rinsed once with distilled water (1 ml) and dried with a cotton ball. The washed area was reoccluded by gluing a second blister on top of the first blister. Radioactivity in each fraction (soap and water wash, rinse, cotton balls) was analyzed by liquid scintillation spectrometry (described later).

Five days posttreatment, each animal was lightly anesthetized with ether and sacrificed by exsanguination. The plastic blisters, treated skin, and a portion of untreated skin were removed. The skin samples, blood, and carcass were weighed and stored at −70°C until further sampling

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RESULTS

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and analysis for radioactivity could be performed. Each metabolism cage was washed with 100 ml of 0.5% solution of Count Off (NEN Research Products, Boston).

Radioactivity was analyzed by using a Packard Tri-Carb 2660 liquid scintillation system (Packard Instrument Co., Downers Grove, Ill.). The skin washes, applicator, and blister were analyzed for radioactivity by counting the sample after mixing with Insta-Gel (Packard Instrument Co.). Aliquots of urine and the metabolism cage washes were analyzed in a similar manner. The treated and untreated skin and portions of the blood, carcass, and feces were combusted in a Packard Tri-Carb Sample Oxidizer (model B-306, Packard Instrument Co.) using Carbosorb and mixed with Permafluor V (Packard Instrument Co.) prior to analysis for radioactivity.

The results of absorption, distribution, and excretion of chemical-derived radioactivity are expressed as percent of the recovered dose. The recovered dose is defined as the sum of radioactivity washed from the skin 24 h posttreatment, and the cumulative amount of radioactivity excreted in the urine and feces and the amount of radioactivity detected in the blood, skin (treated and untreated), cage wash, and carcass 120 h posttreatment. The total urinary excretion of the chemical includes the 120-h cage wash data. The absorbed dose is defined as the cumulative sum of radioactivity excreted in the urine and feces and the amount of radioactivity in blood, untreated skin, and carcass 120 h posttreatment. Mean group comparisons of the disposition of chemical-derived radioactivity were made after application of the chemical in the solid, aqueous paste, and suspension form to that applied in ethanol. The statistical parameters were determined by using a general linear model with the SAS System (Cary, N.C.) with a significance level of $p \leq .05$.

RESULTS

2-*sec*-Butyl-4,6-dinitrophenol (DNBP)

The disposition data of DNBP-derived radioactivity are shown in Table 1. Recovery of radioactivity ranged from 102 to 110% of the applied dose. Approximately 50% of the recovered dose was absorbed through the skin 120 h after application in each of the forms. Approximately 10% of the absorbed dose was retained in the body (body − carcass + blood + untreated skin) by 120 h, with the major fraction residing in the carcass. Absorption and distribution in the blood, carcass, and untreated skin of DNBP-derived radioactivity were not significantly different after application of the chemical in any form.

Washing the skin 24 h posttreatment removed 40–50% of the recovered dose. No significant differences were observed in the comparison of removal of radioactivity by washing after application of DNBP in any

form (Table 1). Radioactivity remaining at the treatment site at 120 h was approximately 5% of the recovered dose for the ethanol, solid, and aqueous paste applications. DNBP-derived radioactivity remaining at the treatment site was significantly greater after application in suspension form (9% of the recovered dose) than after application in ethanol.

Excretion of DNBP-derived radioactivity was predominantly urinary (Table 1). Approximately 70% of the absorbed dose was eliminated by this route. The urinary excretion profiles (Fig. 1) of DNBP applied in all forms were similar. Approximately 50% of the total radioactivity excreted in the urine after application in all forms was detected by 48 h. With all applied forms of DNBP, cumulative fecal elimination of radioactivity by 120 h (Table 1) was approximately 17% of the absorbed dose. The fecal elimination profiles of DNBP-derived radioactivity were also similar (Fig. 1). The

TABLE 1. Disposition of [^{14}C]-DNBP-Derived Radioactivity at 120 h as Percentage of Recovered Dose in Female Fischer 344 Rats After Dermal Application in Four Physical Forms

Item	Ethanol	Solid	Aqueous paste	Suspension
Absorbed	51.7 ± 3.4[a]	46.2 ± 1.1	46.3 ± 2.5	47.7 ± 5.3
	—	(0.89 ± 0.06[a,b])	(0.90 ± 0.08)	(0.92 ± 0.12)
Body[c]	5.8 ± 0.4	6.1 ± 0.5	6.2 ± 0.6	5.9 ± 0.8
	—	(1.05 ± 0.12)	(1.08 ± 0.13)	(1.02 ± 0.15)
Carcass	4.9 ± 0.3	5.4 ± 0.5	5.3 ± 0.6	5.0 ± 0.7
	—	(1.09 ± 0.12)	(1.08 ± 0.14)	(1.02 ± 0.15)
Blood[d]	0.18 ± 0.01	0.19 ± 0.03	0.20 ± 0.01	0.19 ± 0.03
	—	(1.05 ± 0.14)	(1.09 ± 0.09)	(1.03 ± 0.16)
Untreated skin[d]	<0.1	<0.1	<0.1	<0.1
	—	(1.09 ± 0.10)	(0.96 ± 0.09)	(0.93 ± 0.15)
Treated skin	4.9 ± 1.5	4.1 ± 0.8	6.0 ± 0.5	9.3 ± 2.1
	—	(0.84 ± 0.31)	(1.23 ± 0.40)	(1.89 ± 0.73[e])
Skin wash[f]	43.4 ± 2.9	49.7 ± 1.3	47.7 ± 2.3	43.0 ± 4.2
	—	(1.15 ± 0.08)	(1.10 ± 0.09)	(0.99 ± 0.12)
Urine	36.8 ± 2.4	32.6 ± 0.9	32.6 ± 1.7	33.6 ± 3.7
	—	(0.89 ± 0.06)	(0.89 ± 0.07)	(0.91 ± 0.12)
Feces	9.1 ± 0.7	7.5 ± 0.9	7.4 ± 0.4	8.2 ± 1.3
	—	(0.83 ± 0.07)	(0.82 ± 0.08)	(0.90 ± 0.16)
Recovery[g]	110.0 ± 0.7	106.0 ± 2.0	102.0 ± 1.0	104.0 ± 2.0

[a]Mean ± SE, $n = 4$.
[b]Comparative ratio of respective physical form to ethanol.
[c]Body = carcass + blood + untreated skin.
[d]Percent/gram.
[e]Significantly different from ethanol, $p \leq .05$.
[f]Skin wash at 24 h.
[g]Percent of applied dose.

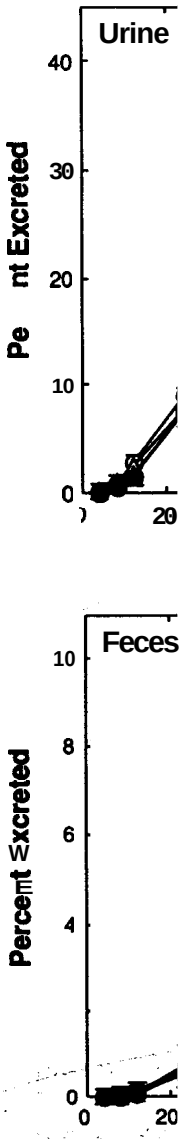


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± 2.5 ± 0.08)	47.7 ± 5.3 (0.92 ± 0.12)
± 0.6 ± 0.13)	5.9 ± 0.8 (1.02 ± 0.15)
± 0.6 ± 0.14)	5.0 ± 0.7 (1.02 ± 0.15)
± 0.01 ± 0.09)	0.19 ± 0.03 (1.03 ± 0.16)
1 ± 0.09)	<0.1 (0.93 ± 0.15)
) ± 0.5 3 ± 0.40)	9.3 ± 2.1 (1.89 ± 0.73[e])
7 ± 2.3) ± 0.09)	43.0 ± 4.2 (0.99 ± 0.12)
5 ± 1.7 9 ± 0.07)	33.6 ± 3.7 (0.91 ± 0.12)
4 ± 0.4 2 ± 0.08)	8.2 ± 1.3 (0.90 ± 0.16)
0 ± 1.0	104.0 ± 2.0

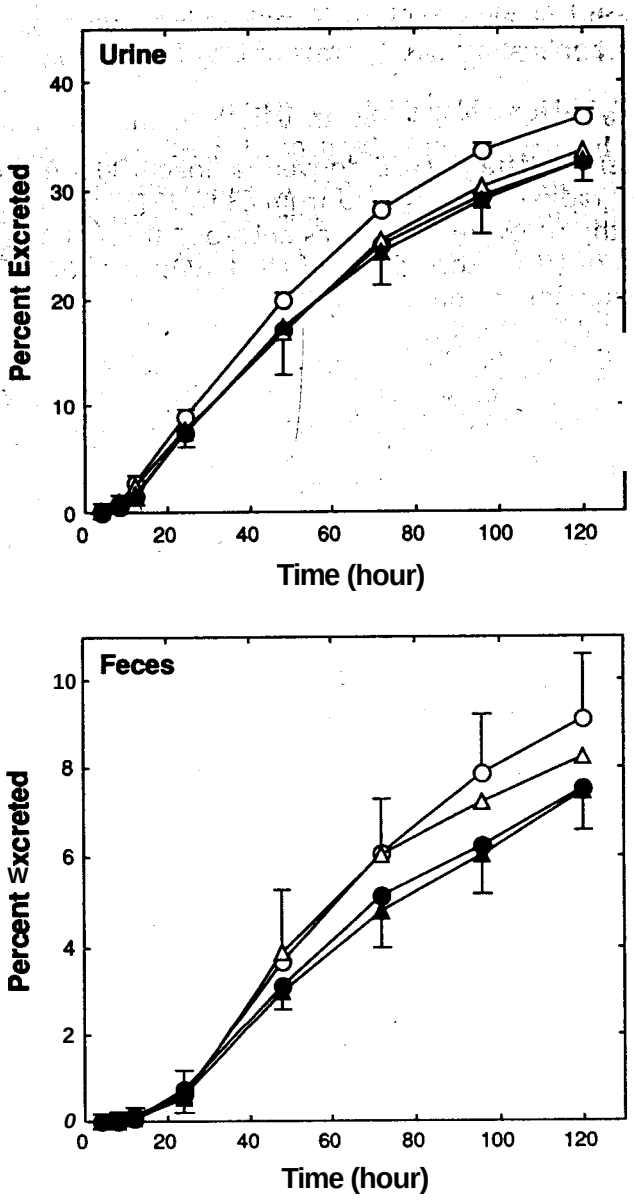


FIGURE 1. Cumulative percent DNBP-derived radioactivity excreted in the urine and feces with respect to time after application in ethanol (○), as a solid (●), as an aqueous paste (▲), or in suspension (△). Data are expressed as mean ± SD, n = 3-4.

total urinary and fecal excretion of radioactivity were not significantly different after application of all forms of DNBP.

2,4,5,2′,4′,5′-Hexachlorobiphenyl (HCB)

The disposition data of HCB-derived radioactivity are shown in Table 2. Recovery of radioactivity ranged from 83 to 101% of the applied dose. Five to 8% of the recovered dose was absorbed through the skin with all applied forms of HCB. Absorption of HCB-derived radioactivity was significantly greater after application as a solid than in ethanol (Table 2). No other significant differences in absorption of HCB were observed. Greater than 92% of the absorbed dose was retained in the body after application of HCB in all forms, with the major portion detected in the carcass. Radioactivity remaining in the body after application as a solid

TABLE 2. Disposition of [^{14}C]-HCB-Derived Radioactivity at 120 h as Percentage of Recovered Dose in Female Fischer 344 Rats After Dermal Application in Four Physical Forms

Item	Ethanol	Solid	Aqueous paste	Suspension
Absorbed	5.3 ± 0.3[a]	8.0 ± 0.2	6.7 ± 0.9	5.9 ± 0.8
	—	(1.50 ± 0.10[a,b,c])	(1.26 ± 0.18)	(1.11 ± 0.16)
Body[d]	5.0 ± 0.3	7.5 ± 0.2	6.2 ± 0.8	5.5 ± 0.7
	—	(1.50 ± 0.11[c])	(1.23 ± 0.18)	(1.10 ± 0.16)
Carcass	5.0 ± 0.3	7.5 ± 0.2	6.1 ± 0.8	5.5 ± 0.7
	—	(1.50 ± 0.11[c])	(1.23 ± 0.18)	(1.10 ± 0.16)
Blood[e]	<0.1	<0.1	<0.1	<0.1
	—	(1.31 ± 0.24)	(1.12 ± 0.28)	(1.23 ± 0.26)
Untreated skin[e]	<0.1	<0.1	<0.1	<0.1
	—	(1.04 ± 0.34)	(1.19 ± 0.25)	(1.17 ± 0.29)
Treated skin	10.4 ± 3.2	10.8 ± 1.1	11.6 ± 8.0	2.6 ± 0.5
	—	(1.04 ± 0.34)	(1.11 ± 0.84)	(0.25 ± 0.09)
Skin wash[f]	84.5 ± 3.5	81.2 ± 0.9	81.8 ± 8.8	91.5 ± 0.4
	—	(0.96 ± 0.04)	(0.97 ± 0.11)	(1.09 ± 0.05)
Urine	<0.1	<0.1	0.2 ± 0.1	<0.1
	—	(1.44 ± 0.34)	(2.93 ± 1.60)	(1.04 ± 0.26)
Feces	0.23 ± 0.02	0.37 ± 0.02	0.32 ± 0.02	0.33 ± 0.08
	—	(1.64 ± 0.15[c])	(1.40 ± 0.15)	(1.47 ± 0.36)
Recovery[g]	101.0 ± 1.0	91.0 ± 0.6	83.0 ± 7.0	93.0 ± 1.0

[a]Mean ± SE, $n = 4$.
[b]Comparative ratio of respective physical form to ethanol.
[c]Significantly different from ethanol, $p \leq .05$.
[d]Body = carcass + blood + untreated skin.
[e]Percent/gram.
[f]Skin wash at 24 h.
[g]Percent of applied dose.

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± 0.8 ± 0.18)	5.5 ± 0.7 (1.10 ± 0.16)
± 0.8 ± 0.18)	5.5 ± 0.7 (1.10 ± 0.16)
1 ± 0.28)	< 0.1 (1.23 ± 0.26)
1 ± 0.25)	< 0.1 (1.17 ± 0.29)
± 8.0 ± 0.84)	2.6 ± 0.5 (0.25 ± 0.09)
± 8.8 ± 0.11)	91.5 ± 0.4 (1.09 ± 0.05)
± 0.1 ± 1.60)	< 0.1 (1.04 ± 0.26)
± 0.02 ± 0.15)	0.33 ± 0.08 (1.47 ± 0.36)
± 7.0	93.0 ± 1.0

was significantly higher than in ethanol (Table 2). No other significant differences in the distribution of HCB-derived radioactivity were observed.

A significant amount of HCB-derived radioactivity was removed by washing the skin. Approximately 80–90% of the recovered dose was removed by this procedure (Table 2). No significant differences were observed in the comparisons of applied forms of HCB in the removal of radioactivity from the treatment site by washing or in radioactivity remaining there by 120 h.

Elimination of HCB-derived radioactivity was primarily via the feces (Table 2), where approximately 5% of the absorbed dose was eliminated. The fecal elimination profiles of HCB-derived radioactivity are shown in Figure 2. Minimal amounts of radioactivity were eliminated in the feces after application in ethanol until 48 h postdosing. Total fecal elimination of radioactivity was significantly higher after application as a solid than in ethanol (Table 2). No other significant differences were observed in the fecal elimination of HCB-derived radioactivity. Elimination of HCB-derived radioactivity in urine ranged from 1.3 to 2.6% of the absorbed dose. The urinary excretion profiles of HCB-derived radioactivity are shown in Figure 2. Except for the two- to threefold increase of radioactivity excreted at 12 h after application of the chemical in aqueous paste form, the overall trend of urinary elimination of this chemical applied in the different forms was similar. No significant differences were observed in the total urinary excretion of HCB-derived radioactivity after application of the chemical in any form.

3,4,3′,4′-Tetrachlorobiphenyl (TCB)

The disposition data of TCB-derived radioactivity are shown in Table 3. Recovery of radioactivity ranged from 63 to 91% of the applied dose. Approximately 6–8% of the recovered dose of TCB-derived radioactivity penetrated the skin after application in the four forms. Retention of radioactivity in the body ranged from 14 to 23% of the absorbed dose by 120 h, with the major portion detected in the carcass. The absorption and distribution of TCB-derived radioactivity were not significantly different after application of chemical in any form (Table 3).

Washing the skin removed 61–91% of the recovered dose. A significantly greater amount of TCB-derived radioactivity was removed from the skin treated with chemical in suspension than in ethanol (Table 3). The treated skin retained a variable amount of radioactivity and was significantly lower after application of TCB in suspension than in ethanol. No other significant differences in TCB-derived radioactivity removed by washing the skin or remaining at the treatment site were observed.

The major route of elimination of TCB-derived radioactivity was via

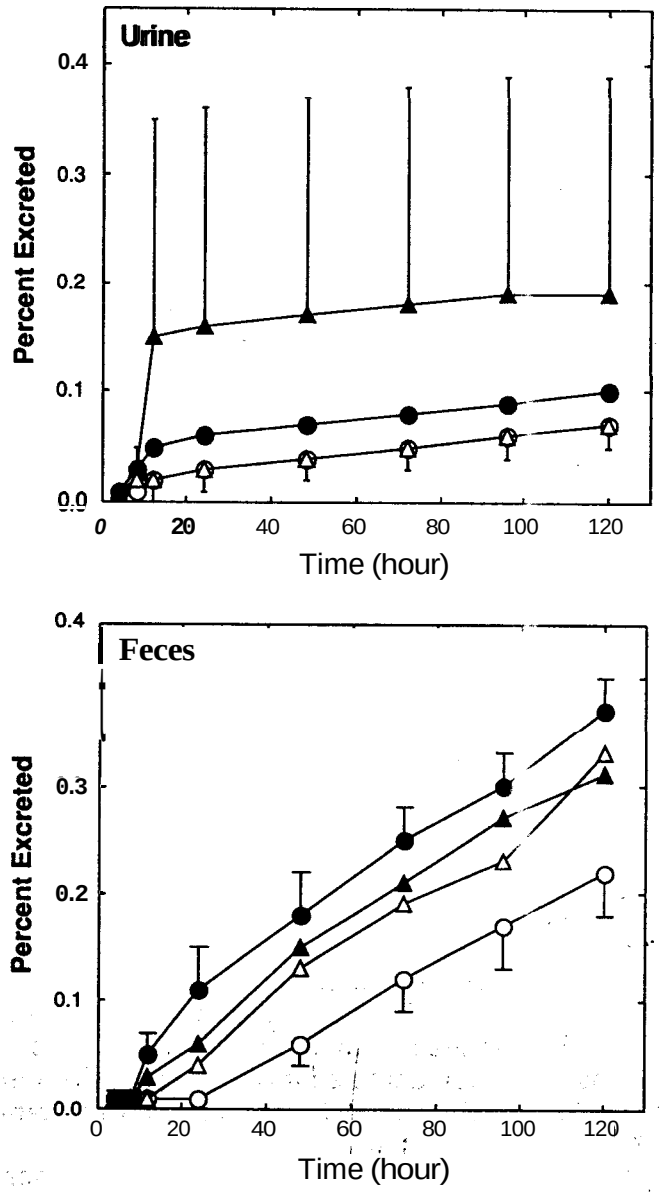


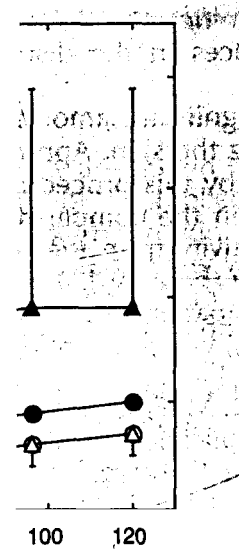
FIGURE 2 Cumulative percent HCBderived radioactivity excreted in the urine, and feces with respect to time after application in ethanol (○), as a solid (●), as an aqueous paste (▲), or in suspension (△). Data are expressed as mean ± SD, n = 3–4.

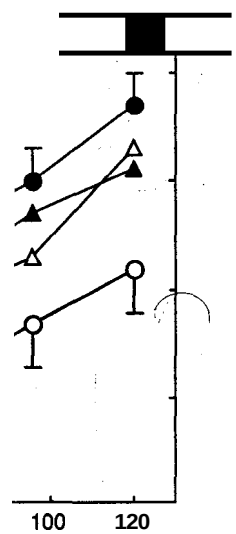
TABLE 3. Disposition of [^{14}C]-TCB-D
Dose in Female Fischer 344 Rats Aft

Item	Ethanol
Absorbed	6.1 ± 1.3[a]
Body[c]	1.5 ± 0.5
Carcass	1.4 ± 0.4
Blood[d]	<0.01
Untreated skin[d]	<0.01
Treated skin	28.9 ± 9.8
Skin wash[f]	65.1 ± 10.7
Urine	0.56 ± 0.07
Feces	4.0 ± 0.8
Recovery[g]	91.0 ± 2.0

[a]Mean ± SE, n = 4.
[b]Comparative ratio of respective
[c]Body = carcass + blood + unt
[d]Percent/gram.
[e]Significantly different from etha
[f]Skin wash at 24 h.
[g]Percent of applied dose.

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as an aqueous paste (▲), or in

TABLE 3. Disposition of [^{14}C]-TCB-Derived Radioactivity at 120 h as Percentage of Recovered Dose in Female Fischer 344 Rats After Dermal Application in Four Physical Forms

Item	Ethanol	Solid	Aqueous paste	Suspension
Absorbed	6.1 ± 1.3[a]	7.8 ± 1.0	7.8 ± 0.7	6.4 ± 0.8
	—	(1.28 ± 0.32[a,b])	(1.29 ± 0.30)	(1.05 ± 0.26)
Body[c]	1.5 ± 0.5	1.6 ± 0.2	1.4 ± 0.2	0.85 ± 0.03
	—	(1.07 ± 0.35)	(0.94 ± 0.32)	(0.57 ± 0.18)
Carcass	1.4 ± 0.4	1.5 ± 0.2	1.4 ± 0.2	0.81 ± 0.03
	—	(1.05 ± 0.35)	(0.94 ± 0.32)	(0.57 ± 0.18)
Blood[d]	<0.01	<0.01	<0.01	<0.01
	—	(1.32 ± 0.43)	(1.23 ± 0.41)	(0.63 ± 0.23)
Untreated skin[d]	<0.01	<0.01	<0.01	<0.01
	—	(1.33 ± 0.39)	(1.09 ± 0.32)	(0.77 ± 0.22)
Treated skin	28.9 ± 9.8	31.0 ± 10.8	17.0 ± 6.4	2.6 ± 1.1
	—	(1.07 ± 0.52)	(0.59 ± 0.30)	(0.09 ± 0.054
Skin wash[f]	65.1 ± 10.7	61.2 ± 11.0	75.2 ± 6.4	91.0 ± 1.5
	—	(0.94 ± 0.23)	(1.15 ± 0.21)	(1.40 ± 0.234
Urine	0.56 ± 0.07	0.75 ± 0.07	0.73 ± 0.05	0.56 ± 0.08
	—	(1.34 ± 0.26)	(1.30 ± 0.24)	(1.00 ± 0.23)
Feces	4.0 ± 0.8	5.4 ± 0.7	5.7 ± 0.5	4.9 ± 0.7
	—	(1.35 ± 0.32)	(1.42 ± 0.30)	(1.23 ± 0.29)
Recovery[g]	91.0 ± 2.0	82.0 ± 0.6	78.0 ± 4.0	63.0 ± 12.0

[a] Mean ± SE, n = 4.
[b] Comparative ratio of respective physical form to ethanol.
[c] Body = carcass + blood + untreated skin.
[d] Percent/gram.
[e] Significantly different from ethanol, $p \leq .05$.
[f] Skin wash at 24 h.
[g] Percent of applied dose.

the feces (Table 3). A range of 68–77% of the absorbed dose was eliminated by this route after application of all forms of TCB. The fecal elimination profiles of TCB-derived radioactivity are shown in Figure 3. Approximately 50% of the absorbed dose of TCB excreted in the feces after application as an aqueous paste was excreted by 48 h, whereas it took approximately 72 h for the ethanol applied TCB to reach this same percentage. However, no significant differences in the total fecal elimination of radioactivity were observed after application of TCB in any form (Table 3). Elimination via the urine amounted to approximately 9–10% of the absorbed dose with all forms of applied TCB. The urinary elimination profiles of TCB-derived radioactivity are shown in Figure 3. No significant differences were observed in the total urinary elimination of TCBderived radioactivity applied in any form (Table 3).

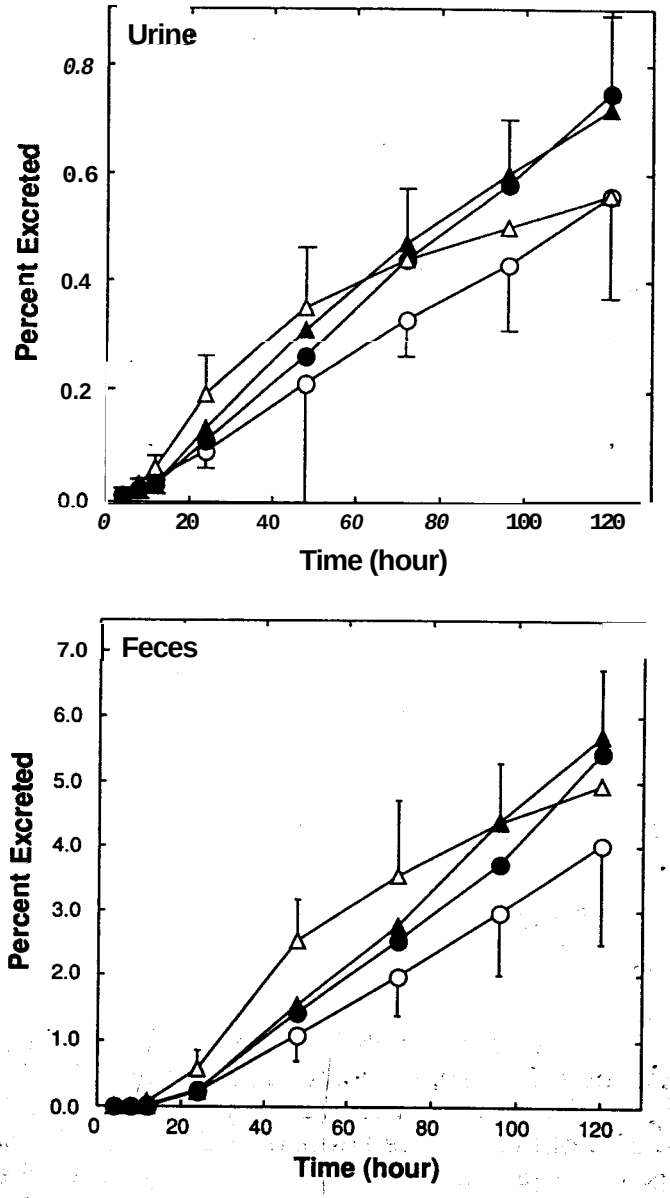


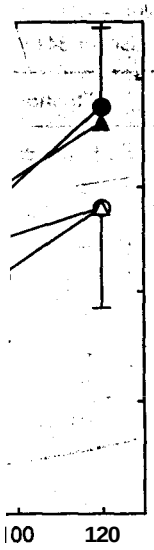
FIGURE 3. Cumulative percent TCB derived radioactivity excreted in the urine and feces with respect to time after application in ethanol (○), as a solid (●), as an aqueous paste (▲), or in suspension (△). Data are expressed as mean ± SD, $n = 3$–4.

DISCUSSION

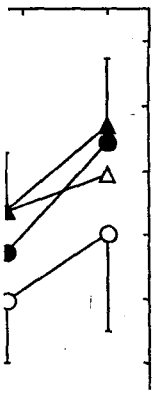
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DISCUSSION

Dermal absorption of the DNBP, HCB, and TCB applied as a solid, aqueous paste, suspension, or in the volatile vehicle ethanol to female rat skin was observed. Among the three chemicals applied as a solid, only the absorption of HCB was significantly greater compared to its absorption after application in ethanol. However, this increase may not be that biologically meaningful, due to the low percentage (<10%) of HCB-derived radioactivity absorbed in both cases. Chemical application as an aqueous paste or suspension had no significant effect on the absorption of the compounds examined. Even though the chemicals have low water solubilities of 100 ppm or less and additional water was present in their formulations, some fraction was able to become solubilized and penetrate the skin. Thus, the dermal exposure to these chemicals in the various physical forms investigated appears to result in equivalent absorption through the skin. Individuals exposed to these chemicals in various forms, which may occur in agricultural, industrial, or waste site settings, may have the same risk for absorption when contacted on their skin.

The method of application of the chemicals with the Teflon disc in this study requires consideration. Dermal absorption of chemicals is increased if the skin is damaged (Bronaugh and Stewart, 1985). The flexible Teflon disc with chemical was rubbed onto the skin for approximately 5 s, and one may propose that the physical contact and rubbing action may have damaged the stratum corneum. However, no damage to the skin was observed visually after rubbing it. Also, absorption of the chemicals was significantly increased in only one out of nine groups (solid, aqueous paste, and suspension) that were rubbed with the applicator when compared to the application of the chemical in ethanol. McMaster et al. (1985) have reported no significant differences in skin absorption of cortisone in an ointment when it was rubbed onto the skin with 100 strokes with a metal spatula compared to spreading on the ointment. Thus the method of chemical application with the Teflon disc does not appear to have any overall effect on absorption of the chemicals, but additional studies to examine this are required.

Washing the skin 24 h postapplication had a significant effect on the dermal absorption of the chemicals. A range of 43-91% of the recovered dose for the 3 chemicals was removed by washing. In previous studies in our laboratory, the dermal absorption of HCB (Fisher et al., 1989) and DNBP (Hall et al., 1992) was examined in rats without washing the treated skin. In these studies, 43 and 95% of the recovered dose of HCB and DNBP, respectively, was absorbed by 120 h after application. In the Present study with the washing procedure, approximately 8 and 52% of the recovered dose of HCB and DNBP, respectively, applied in all four forms was absorbed. Thus, washing the skin removed significant

amounts of the chemical that could have penetrated the skin and distribute throughout the body. Our results of washing differ from those reported by Wester et al. (1983) for guinea pigs treated with a complex mixture of polychlorinated biphenyls. Their washing method consisted of *2* washes with distilled water and *2* with acetone either immediately after dosing or **24** h postdosing. This method removed only 60% of the dose immediately after application and *20%* or less at **24** h. Thus, the specific chemical and vehicle applied, species, the washing procedure, wash constituents, and the amount of chemical absorbed all have an impact on the ability to remove the chemical from the treatment site. Individuals dermally exposed to these chemicals may have reduced risk of absorption and potential toxic effects if they wash themselves thoroughly after contact with the chemical.

Dermal absorption of DNBP, HCB, and TCB applied in different forms was observed in this study. Except for HCB applied as a solid, there were no significant differences in the absorption of the chemicals when applied in these forms. This study suggests that dermal exposure of these specific chemicals in solid, aqueous paste, or suspension forms may involve the same level of risk for absorption and potential systemic toxic effects as when exposed to the chemical dissolved in the volatile vehicle ethanol.

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