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Hairless Mice as Models for Chloracne: A Study of Cutaneous Changes Induced by Topical Application of Established Chloracnegens

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Hairless Mice as Models for Chloracne: A Study of Cutaneous Changes Induced by Topical Application of Established Chloracnegens. PUHVEL, S. M., SAKAMOTO, M., ERTL, D. C., AND REISNER, R. M. (1982). *Toxicol. Appl. Pharmacol.* **64,** 492–503. Two types of hairless mice, one from the inbred strains, HRS/J, and the other from the outbred stock, Skh:HR-1, were used to study the feasibility of inducing experimental chloracne with various well-established chloracnegens. Animals were treated topically for periods ranging from 2 to 10 weeks, and the cutaneous changes were monitored. Most chloracnegens induced a distinct pattern of cutaneous pathology, but this pattern did not include hyperkeratinization of the sebaceous follicles, which is considered the pathognomonic lesion in human chloracne. Rather, the changes induced by chloracnegens such as Halowax 1014, N-wax-34, Phenclor 54, and 2,3,4,8-tetrachlorodibenzo-*p*-dioxin were: epidermal hyperkeratosis and hyperplasia, loss of sebaceous glands, keratinization of intradermal pilar cysts, and, often, diffuse lymphohistiocytic infiltration of the dermis. Only one chloracnegen, 3,4,3′,4′-tetrachlorobiphenyl, induced a true chloracne-like syndrome, and only in one of the strains of mice (Skh:HR-1). This syndrome involved massive hyperkeratosis of the sebaceous follicles and hyperkeratinization of intradermal pilar cysts. In many instances, these cysts spontaneously ruptured into the dermis and induced the development of pimple-like foci of inflammatory cell accumulation in the skin. All animals developing these cutaneous changes also underwent a generalized metabolic disturbance resulting in gross weight gain, primarily due to large intraabdominal fat deposits.

Development of chloracne is considered the most sensitive indicator of human poisoning by polyhalogenated aromatic hydrocarbons (Moore, 1978). Levels of chloracnegenic compounds, which may be insufficient to cause detectable systemic changes, have been observed to cause mild to moderate chloracne in skin of exposed subjects. This finding suggests that sebaceous follicles are extremely receptive target organs for this group of chemicals.

An animal model would greatly facilitate the study of the biochemical changes in skin induced by chloracnegen exposure. In the literature, three animals have been cited for their usefulness in this regard: The inner surface of the rabbit external ear (Hambrick and Blank, 1956; Adams *et al.*, 1941); the facial skin of rhesus monkeys (McConnell *et al.*, 1978; McNulty *et al.*, 1980, 1981), and the skin of hairless mice (Inagami *et al.*, 1969). Of these, the hairless mouse model seemed the most appealing for practical reasons of economy and ease of safe maintenance of contaminated animals. However, even though this species is consistently referred to as an experimental model for chloracne (Kimbrough, 1974; Knutson and Poland, 1980; Poland and Glover, 1980; Crow, 1981), to our knowledge, published descrip-

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TABLE 1

TREATMENT SCHEDULE OF MICE WITH CHLORACNEGENS

Chemical	Duration of treatment
Halowax 1014	29 mg, three times a week for 2 weeks
Halowax N-34	20 mg, five times a week for 2 weeks
Octachloronaphthalene	20 mg, five times a week for 2 weeks
Arochlor 1254	(a) 50 mg, one time (fatal) (b) 1 mg, four times a week for 6 weeks (c) 8 mg, four times a week for 6 weeks
Phenclor 54	0.2 mg, five times a week for 10 weeks
TCB	0.2 mg, five times a week for 10 weeks
TCDD	0.1 μg, three times a week for 4 weeks[a]

[a] This dosage and schedule of TCDD application were suggested by Dr. Alan Poland (McCardle Cancer Institute, Madison, Wisc.).

tions of its use have appeared only in Japanese.

In 1969, Inagami *et al.* (1969) reported that follicular hyperkeratotic changes were induced in sebaceous follicles of hairless mice following po administration of Kenachlor-contaminated rice oil. Kenachlor, a polychlorinated biphenyl (PCB), was the cause of the most extensive episode of human poisoning by a chloracnegen. In Southwest Japan in 1968, over 1200 subjects developed signs of chloracne and related systemic poisoning following the ingestion of rice oil accidentally contaminated by this PCB (Kuratsune, 1971; Goto and Higuchi, 1969). Nagayama *et al.* (1976) later showed that the Kenachlor was contaminated by 5 ppm of polychlorinated dibenzofurans, and the latter substances were the more potent chloracnegens.

The present report evaluated the usefulness of hairless mice as models for studying the effects of topical application of several different classes of polychlorinated aromatic hydrocarbons.

METHODS

Animals. Two strains of hairless mice were used: Skh:HR-1, originally obtained from the Skin and Cancer Hospital in Philadelphia, Pennsylvania; and HRS/J from the Jackson Laboratories (Bar Harbor, Maine). Female mice, 10 to 12 weeks old at the beginning of treatment, weighing approximately 20 to 25 g were used in this study. Animals were distributed randomly into treatment groups of three animals per group.

Chemicals. The following compounds were tested.

1. Polychlorinated naphthalenes
   Halowax 1014
   Halowax N-34
   Octachloronaphthalene
2. Polychlorinated biphenyls (PCBs)
   Aroclor 1254
   Phenclor 54
   3,4,3′,4′-Tetrachlorobiphenyl (TCB)
3. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)

Chlorinated naphthalenes were a gift from Dr. Robert Cuozzo, Chemisphere Company; PCBs were obtained from Analabs; and TCDD from KOR, Inc. All chemicals were dissolved in acetone and applied to the dorsal skin of mice in 0.1-ml volumes, either in pure acetone solutions or in acetone:mineral oil (4:1) emulsions (0.01% Tween 80 was the emulsifying agent).

Treatment. Concentrations and duration of application of the various chemicals are listed in Table 1. Mice treated with vehicle alone constituted control groups. For safety reasons, all animals were maintained in a laboratory chemistry hood for the duration of the experiments. Mice treated with TCDD were maintained in a Biohazard Safety Containment box (Class III glove box). Animals were kept in plastic cages on standard hardwood bedding and fed Wayne Lablox (Universal Feeds, Inc. Colton, Calif.) *ad libitum* until the time they were killed. Gross observations were made daily and punch biopsies of treated skin were taken for histologic observation at regular intervals. At the end of treatment periods, mice were killed by cervical dislocation and necropsies performed.

Aryl hydrocarbon hydroxylase (AHH) induction and assay. When differences in responsiveness to chloracnegens were found in the two strains of mice (see Results), experiments were set up to compare the innate as well as the inducible AHH in the epidermis of the two strains. Mice from both strains were divided into three groups. One group was treated topically with 0.2 mg of TCB in 0.1 ml acetone for 2 consecutive days. The other was treated with 0.1 μg of TCDD in 0.1 ml

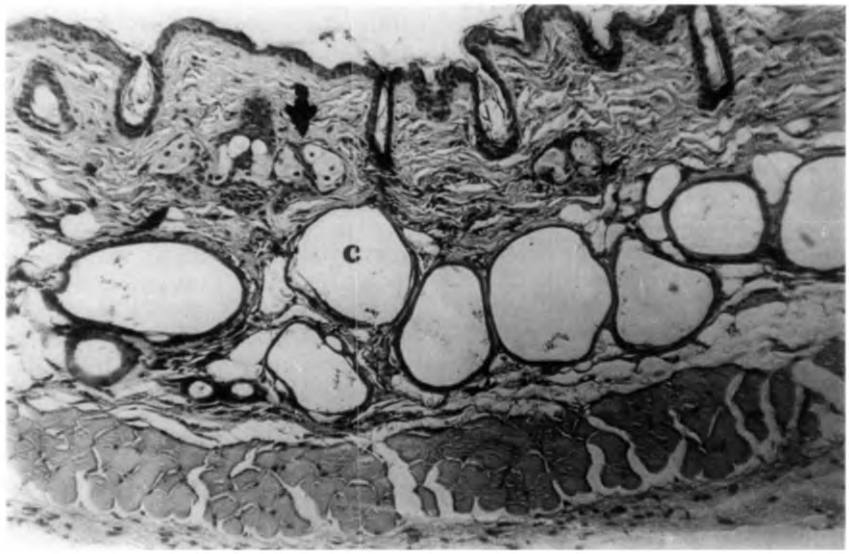

FIG. 1. Normal histology of hairless mouse skin. Note presence of sebaceous glands (see arrow), as well as numerous empty pilar cysts (see "c") in the lower dermis. (×300).

of acetone for 2 consecutive days. The third group, constituting control animals, received topical application of 0.1 ml of acetone for 2 consecutive days. Twenty-four hours after the last treatment, the animals were killed by cervical dislocation, and the dorsal skins were removed. Separation of epidermis from the dermis was facilitated by heat–cold treatment of whole skin (Thompson and Slaga, 1976). Following this treatment the epidermis was scraped from the dermis and pooled for each group in 0.5-ml volumes of homogenizing solution. AHH activity was assayed according to the methods previously described by Kinoshita and Gelboin (1972) and Bowden *et al.* (1974). Benzo [*a*] pyrene was used as substrate, and AHH activity was measured as the amount of 3-hydroxybenzo [*a*] pyrene formed in 30 min/mg of protein in the homogenate.

RESULTS

The normal histology of the hairless mouse skin was similar in both the Skh:HR-1 and HRS/J animals (Fig. 1). The epidermis was thin, consisting of two or three cell layers. The lower dermis contained numerous empty pilar cysts. Sebaceous follicles were well defined, evenly distributed throughout the dorsal skin. These multilobulated structures emptied to the skin surface through distinct follicular ducts (Fig. 2). Topical applications of acetone, or acetone:mineral oil (4:1) emulsions, had no detectable effect on the cutaneous morphology of the control animals.

Polychlorinated Naphthalenes

Mice treated with Halowax 1014 and N-34 developed hyperkeratotic scaly skin within 14 days of treatment. Follicular involvement could not be detected grossly. At the histologic level, hyperkeratosis and epidermal hyperplasia, sebaceous gland involution, and intraepidermal keratinous cyst formation were evident by 14 days. Octachloronaphthalene, which is not a chloracnegen in other systems, did not induce gross or histologic changes in hairless mouse skin, suggesting that the changes induced by Halowax 1014 and N-34 were related to their structural configuration.

Polychlorinated Biphenyls

Aroclor 1254. A single topical application of 50 mg of Aroclor 1254 was fatal to hairless mice within 24 hr.

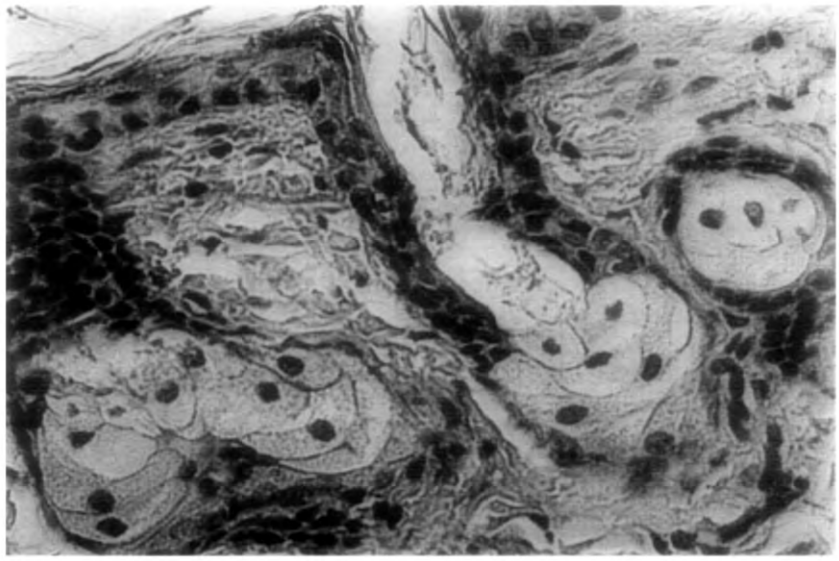

FIG. 2. Detail of normal sebaceous gland in skin of untreated hairless mouse. (×1350).

Dosages of 1 and 3 mg of Aroclor 1254, four times a week for 6 weeks, induced no observable changes, either grossly or histologically.

Phenclor 54. After 10 weeks of treatment with Phenclor 54, the skin of the treated animals appeared grossly normal. Histology revealed stratum corneum hyperkeratosis and epidermal hyperplasia, disappearance of sebaceous glands, and presence of numerous intradermal keratinous cysts (Fig. 3). Necropsy failed to demonstrate abnormalities in internal organs.

3,4,3',4'-Tetrachlorobiphenyl (TCB). This compound has been described as a potent chloracnegen in the rabbit ear bioassay (S. B. Tucker, personal communication). In hairless mice, application of 0.2 mg TCB five times a week did not induce grossly visible changes by 4 weeks of treatment. However, at the microscopic level, epidermal hyperplasia and disappearance of sebaceous glands could be seen in the Skh:HR-1 strain of mice (but not in the HRS/J strain) by 4 weeks. After 6 weeks of treatment, careful examination of the Skh:HR-1 strain (but not the HRS/J strain) of animals revealed the appearance of pinhead-sized whitish spots in the skin. These progressively increased in number and size. At the same time, these animals showed marked weight gain. By 10 weeks of treatment, the animals were grossly fat and the skin was covered by whitish spots (Fig. 4). Necropsy revealed large mesenteric intraabdominal fat deposits (Fig. 5). Histologically, by the eighth week, the skin of these animals showed marked follicular hyperkeratosis. The sebaceous glands, which had disappeared earlier, remained absent, but sebaceous follicles were distended with keratin (Fig. 6). Intradermal pilar cysts had undergone differentiation into keratinous cysts, and as a result, the dermis was full of such keratin-filled structures (Fig. 7). Biopsy and histologic examination of what was grossly a whitish pinhead-sized lesion in the skin indicated that in this area the keratinous cysts had ruptured into the dermis, and these lesions consisted of dense infiltrates of predominantly polymorphonuclear leukocytes (Fig. 8).

The HRS/J strain of mice had an entirely different reaction to TCB treatment than did the Skh:HR-1. After 10 weeks of treatment, these animals (HRS/J strain) showed no marked weight gain. Their skin was shiny,

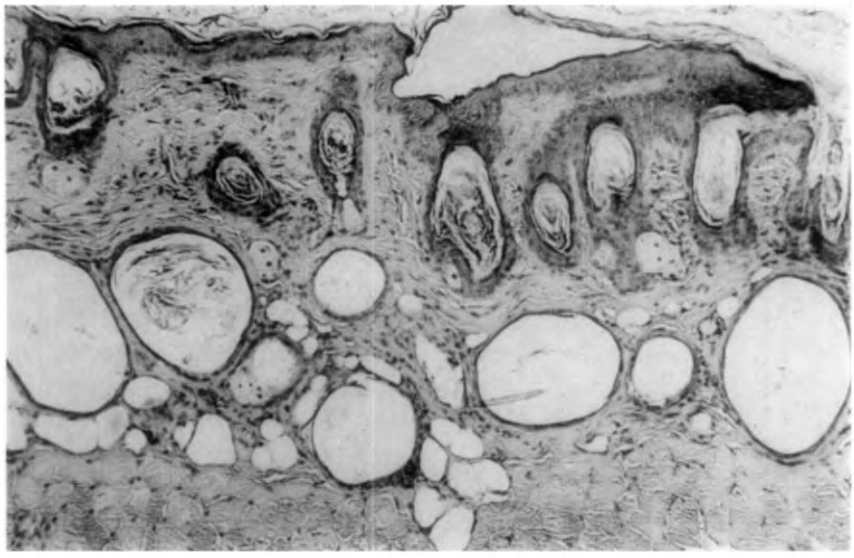

FIG. 3. Skin of Skh:HR-1 mouse treated with 0.2 mg of Phenclor 54, five times a week for 10 weeks. Note epidermal hyperkeratosis and mild hyperplasia, absence of sebaceous glands, and presence of infundibular and intradermal cysts. (×300).

with fine hyperkeratotic scales (Fig. 9). No whitish cysts were present. Histologically, the prominent changes were stratum corneum hyperkeratinization, epidermal hyperplasia, absence of sebaceous glands and follicles, and keratin buildup in the dermal cysts (Fig. 10).

TCDD. Topical application of 0.1 μg of TCDD three times a week induced erythema and scaliness in skin of both strains of hair-

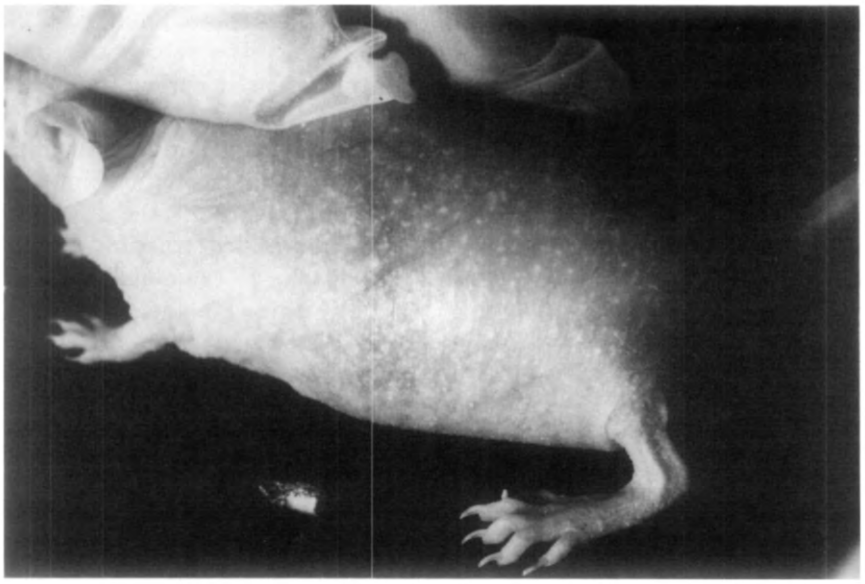

FIG. 4. Skh:HR-1 mouse after 10 weeks of topical treatment with 3,4,3′,4′-tetrachlorobiphenyl (TCB). Note weight gain and presence of whitish pinheadsized spots over entire skin.

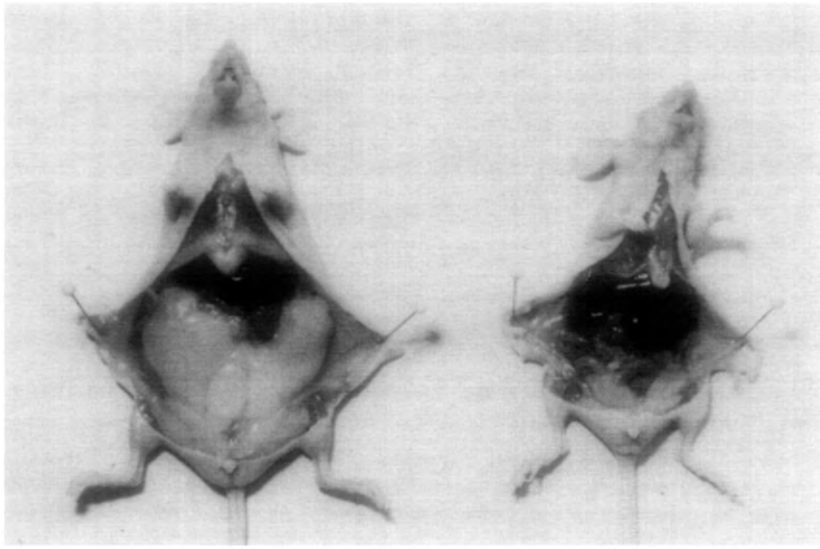

FIG. 5. Necropsy of Skh:HR-1 mouse after 10 weeks of treatment with TCB. Note mesenteric fat deposits. Acetone-treated control on right side.

less mice after six applications. This appearance progressed to a marked scaliness in the HRS/J strain by the end of the fourth week (Fig. 11). In the Skh:HR-1 strain, the skin became hard and shiny; the scaliness was finer and generally resembled the TCB-treated HRS/J mice.

Histologically, the changes in both strains

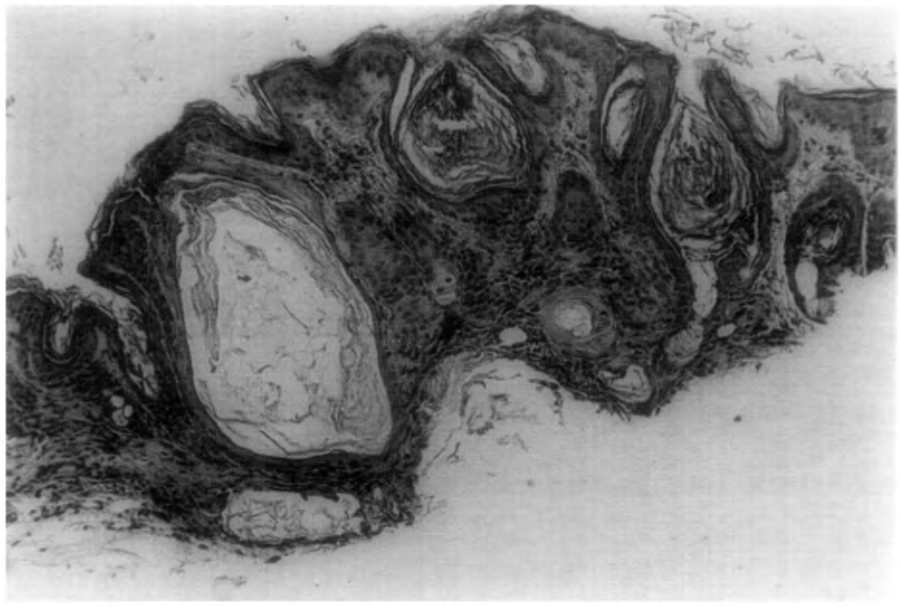

FIG. 6. Cross section of skin of Skh:HR-1 mouse after 10 weeks of TCB treatment. Note follicular hyperkeratosis, absence of sebaceous glands, and mild epidermal hyperplasia. (×300).

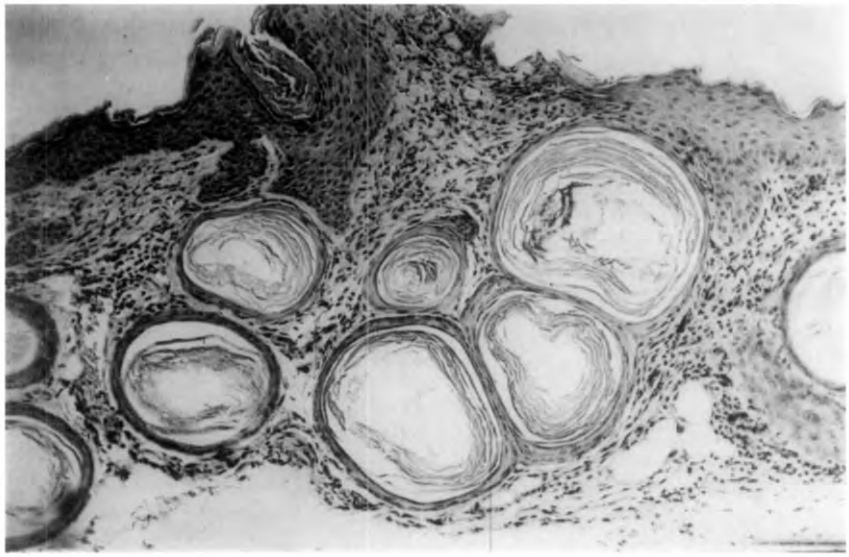

FIG. 7. Another cross section of TCB-treated Skh:HR-1 mouse skin. Note the keratin-filled cysts in the dermis. (×300).

of mice resembled those induced by TCB treatment of HRS/J mice, hyperkeratinization of the stratum corneum, epidermal hyperplasia, absence of sebaceous glands and follicles, and keratin buildup in the dermal cysts. In addition, TCDD induced the presence of a diffuse limphohistiocytic infiltrate in the dermis (Fig. 12).

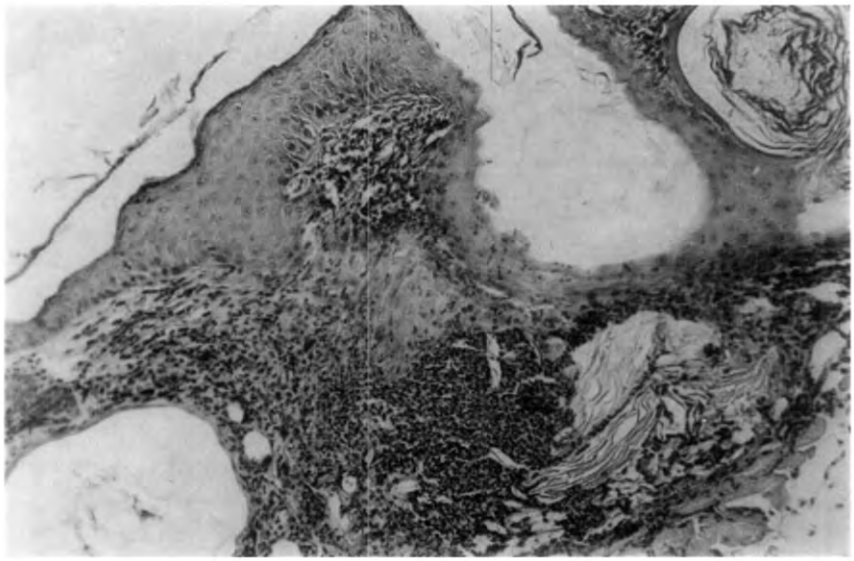

FIG. 8. Further illustration of TCB-treated skin of Skh:HR-1 mouse. Section is through a pinhead-sized, white spot and shows that this change is a localized inflammatory reaction resulting from the spontaneous rupture of a keratinous dermal cyst. (×300).

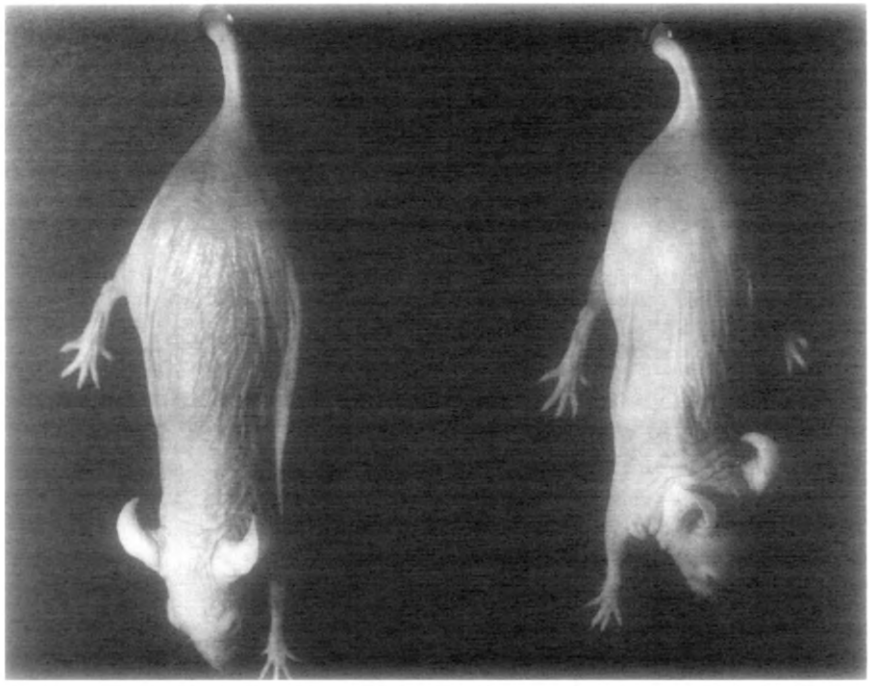

FIG. 9. HRS/J mouse treated with TCB for 10 weeks (on left). Note shiny, scaly skin. No abnormal weight gain. Untreated HRS/J mouse is on right.

Aryl hydrocarbon hydroxylase activity. Results of the AHH assays are summarized in Table 2. Although the basal activity and the induction ratio (induced AHH activity/basal AHH activity) with TCB was roughly the same in both strains of mice, the induc-

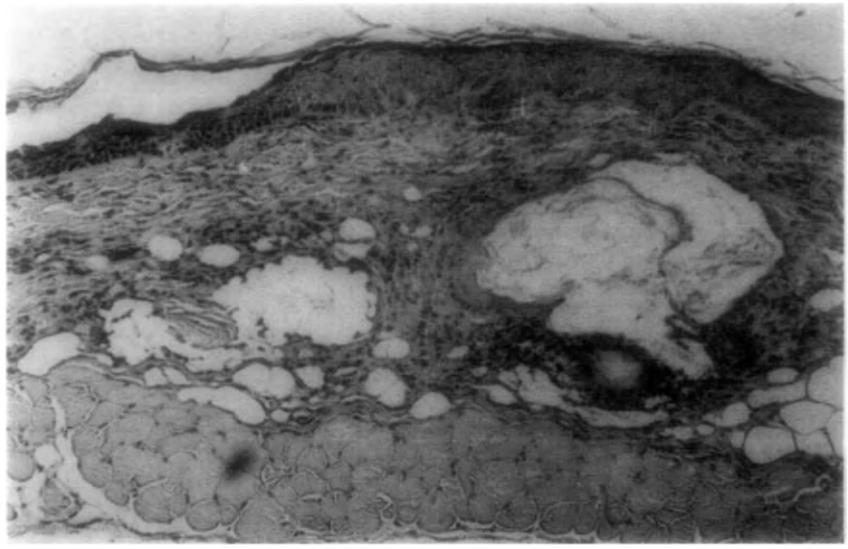

FIG. 10. Cross section of skin of TCB-treated HRS/J mouse. Note epidermal hyperplasia, hyperkeratinization, and keratin-filled intradermal cysts. (×300).

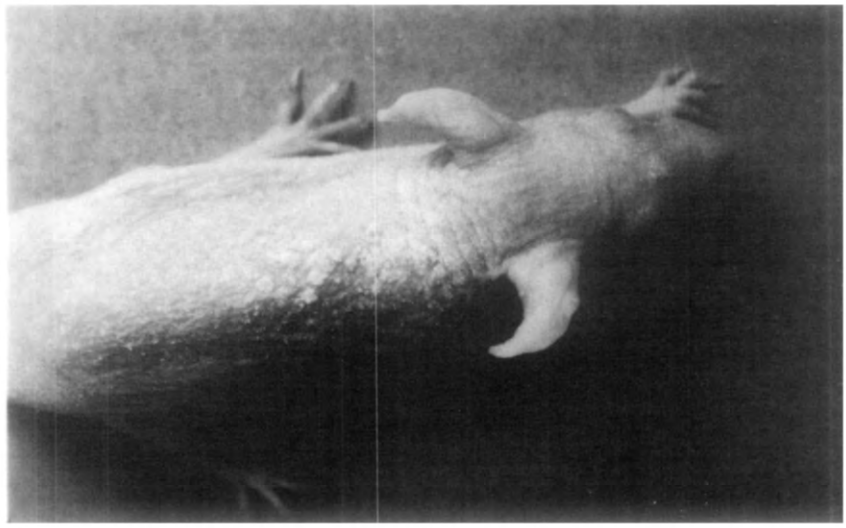

FIG. 11. HRS/J mouse treated with 0.1 mg of TCDD, three times a week for 4 weeks.

tion ratio with TCDD in the HRS/J animals was more than twice that of Skh:HR-1 strain mice.

DISCUSSION

Theoretically, skin of hairless mice should be an ideal model in which to study chloracne. In these animals, hair follicles are rudimentary and very sparse. Sebaceous follicles are evenly distributed, multilobular structures emptying into distinct follicular ducts (Figs. 1 and 2). However, it became apparent very soon in this study that sebaceous follicles in hairless mouse skin are not as sensitive to keratinizing stimuli as are sebaceous follicles in rabbit ear skin. In rabbit ears, grossly visible follicular hyperkeratotic changes are induced by chloracnegens within 2 weeks of treatment. In hairless mice, epidermal hyperplasia and hyperkeratinization can easily be induced in this time period, but follicular hyperkeratosis, when it occurs, requires 6 to 8 weeks of treatment. Nevertheless, hairless mice have some advantages over rabbits. Chloracnegens are invariably biohazards. The most potent ones, such as TCDD and dibenzofurans, are extremely toxic and require use of special biohazard facilities. For laboratories lacking appropriate animal care areas for maintenance of exposed animals, the hairless mouse has the advantage in size. Cages can be fitted into biohazard glove boxes in the laboratory.

In this animal model, there were two distinct patterns of response to topical chloracnegen application. The most frequently effected response in our experience consisted of a combination of epidermal hyperplasia

TABLE 2

RESULTS OF ARYL HYDROCARBON HYDROXYLASE ASSAY

Strain	Treatment	AHH activity[a]	Induction ratio[b]
Skh:HR-1	Control	0.54	
	TCB	6.11	11.23
	TCDD	12.50	22.97
HRS/J	Control	0.35	
	TCB	4.11	11.67
	TCDD	18.60	52.84

[a] AHH activity expressed as nM of 3-hydroxybenzo[*a*]pyrene formed/mg of protein in the epidermal homogenate/30 min (nM 3-OH-BP/mg/30 min).

[b] Induction ratio is the induced AHH activity divided by the basal AHH activity.

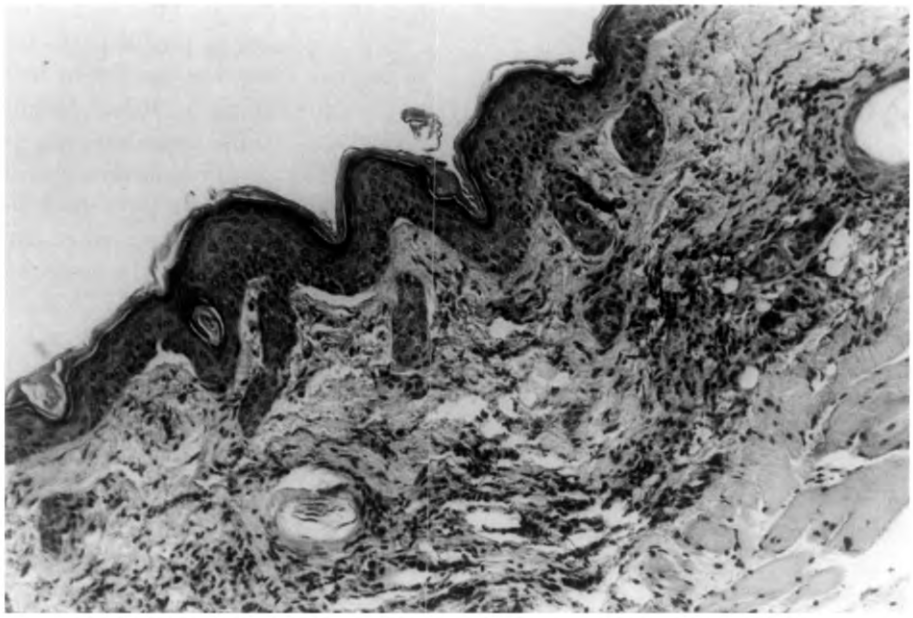

FIG. 12. Cross section of HRS/J mouse skin following 4 weeks of TCDD treatment. Note epidermal hyperplasia, hyperkeratinization, squamous metaplasia of sebaceous follicles, and lymphohistiocytic infiltrate in the dermis. (×300).

and hyperkeratinization, disappearance of sebaceous glands, occasional squamous metaplasia of the sebaceous follicles, and differentiation of the epithelial lining of dermal cysts to a pattern of keratin production. The other response, found with only one strain of mice (Skh:HR-1) and with only one compound (TCB) in the present study, was different in that, in addition to the epidermal changes, follicular hyperkeratinization and hyperkeratinization of dermal cysts were very dramatic. In addition, the cystic keratinization resulted in spontaneous rupture of these keratin-filled structures into the dermis, inducing localized pericystic inflammatory lesions reminiscent of changes effected in human skin in clinical chloracne. This second pattern of cutaneous change was accompanied by marked increase in the weight of these animals, suggesting systemic metabolic disturbances, presumably resulting from liver damage. Such a pattern of weight gain is just the opposite of what has been previously reported in animal toxicity studies with halogenated aromatic hydrocarbons. Weight loss and general wasting are more common findings. Thus, the finding of weight gain warrants further study to define the cause.

There has been some debate over the sequence of events in human chloracne. One suggestion has been that chloracnegens localize in sebaceous glands and effect a change in the lipid metabolism of these structures (Cunliffe *et al.*, 1975) with the result that more "comedogenic" sebaceous lipids are produced, and these in turn induce the follicular hyperkeratinization resulting in comedo formation and chloracne. The present work does not support this theory. In hairless mouse skin, sebaceous follicles are uniformly sensitive to the suppressive effects of chloracnegens. One of the most consistent changes induced by all the effective chloracnegens in the present study was early disappearance of sebaceous glands. This change occurred even in the Skh:HR-1 mice treated with TCB. A 4 weeks of treat-

ment, sebaceous glands had disappeared even though follicular hyperkeratinization occurred several weeks later. This change suggests that the follicular hyperkeratinization is an extension of the epidermal response and not related to metabolic changes in sebaceous glands. These same conclusions were reached by Passi *et al.* (1981) after lipid analysis of TCDD-induced human chloracne lesions. The lipid composition of comedones in human chloracne reflected epidermal, rather than sebaceous gland, origin.

The finding that Aroclor 1254 was ineffectual as a chloracnegen was not entirely surprising. Vos and Beems (1971), in a study of comparative dermal toxicity of Phenclor DP6, Clophen A60, and Aroclor 1260, found the Aroclor to have least dermal toxicity of the three compounds. This low degree of dermal toxicity was attributed to the low level of contaminating penta- and tetrachlorodibenzofurans in Aroclor 1260 compared to higher levels in the other two compounds (Vos and Beems, 1971). In the present study, we did not analyze Aroclor 1254 to determine the concentration of contaminating dibenzofurans, but our findings corroborated those of Vos and Beems (1971) using rabbits, in that we found Aroclor 1254 to be an ineffective chloracnegen in the hairless mouse model and Phenclor to induce well-defined histologic changes.

At this point, we cannot explain why the HRS/J and the Skh:HR-1 animals reacted so differently to TCB. All animals were treated at the same time with the same preparations of TCB, in identical doses. Genetically, the mice came from two distinct stocks. There are many loci in mice which control alopecia, and the term "hairless" refers to a specific gene on chromosome 14. Thus, although both the Skh:HR-1 and HRS/J mice carry the same allele at the hr locus, there are probable differences in genetic background at other loci. HRS/J mice are an inbred strain; Skh:HR-1 come from an outbred stock and, thus, probably have more genetic variability. Despite this difference, the response to TCB and other chloracnegens induced in the Skh:HR-1 mice in the present study was consistent in all animals tested with each specific chemical.

Studies of mouse responsiveness to polyhalogenated aromatic hydrocarbons, of which TCDD is the prototype, have divided strains into genetically predetermined responsive or unresponsive strains on the basis of AHH inducibility (Poland *et al.*, 1974; Poland and Glover, 1976). In the present study, both strains of mice were responsive to AHH induction. The HRS/J strain had a higher AHH response following TCDD administration than the Skh:HR-1 animals, but the responsiveness to TCB was the same in both strains.

This finding of such dramatic differences in clinical response between animals of the same species may serve as a tool in future studies for elucidating the biochemical markers which determine vulnerability to the cutaneous, as well as the systemic, effects of certain chloracnegens.

ACKNOWLEDGMENTS

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