STUDIES WITH CHLORINATED DIBENZO-p-DIOXINS, POLYBROMINATED BIPHENYLS, AND POLYCHLORINATED BIPHENYLS IN A TWO-STAGE SYSTEM OF MOUSE SKIN TUMORIGENESIS POTENT ANTICARCINOGENIC EFFECTS*

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The chlorinated dibenzo-p-dioxins and chlorinated dibenzo-furans are among the most potent teratogens and toxins that are found as environmental contaminants. The polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs) are not nearly as toxic as the dioxins but they are environmentally more prevalent than the dioxins. Both classes of compounds are inducers of the cytochrome P_{1-2}-mediated microsomal monooxygenases[illegible] and of δ-aminolevulinic acid synthetase. The dioxins induce aryl hydrocarbon hydroxylase (AHH, E.C. 1.14.14.2), the enzyme system responsible for converting polycyclic aromatic hydrocarbons (PAH) to active and inactive metabolites, much the same as 3-methylcholanthrene (3-MC) but for periods up to 15 days after a single i.p. injection and at much lower doses.[illegible] PCBs and PBBs are mixtures of various isomers and induce the monooxygenase system with properties similar to both phenobarbital and 3-MC but the duration of induction is much shorter than with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).[illegible] The toxicologic response is similar for both classes of compounds in that they are hepatotoxic,[illegible] cause a decreased growth rate[illegible] and produce chloracne in test animals and man.[illegible]

The effects of PCBs on carcinogenicity of various chemicals have been investigated by numerous groups. Kanechlor 500 in combination with several hepatocarcinogens (3-methyl-4-dimethylaminoazobenzene, N-2-fluorenylacetamide and diethylnitrosamine) in the diets of rats markedly decreased the formation of hepatocarcinomas. Kimura *et al.*[illegible] demonstrated that pretreatment with Kanechlor 400 in diets of rats 4 months prior to and 2 months during treatment with 3-methyl-4-dimethylaminoazobenzene protected the rats against the formation of hepatocarcinomas induced by this carcinogen. Treatment of animals with the organochlorine insecticide 1,1,1-trichloro-2,2-bis-(p-chlorophenyl)-ethane (DDT) has been shown to inhibit 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumors.[illegible] These findings as well as other reports[illegible] suggest that in terms of effects on carcinogenesis, timing is important in the application of PCB to the diets of laboratory animals. Treatment with the PCBs prior to the administration of carcinogen results in

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MONS 207488

[illegible] PCBs in these studies were attributed to the antioxidant activity of [illegible] while the enhancement was ascribed to the promoting properties of the PCBs.

The two-stage system of mouse skin tumorigenesis allows one to study the [illegible] the initiation and promotion phases of carcinogenesis in this animal.[4] The initiation phase requires a single subthreshold dose of a genotoxic carcinogen, but the promotion stage requires multiple applications of the [illegible] and is expressed up to a given time point. These two stages of [illegible] effects of modifiers on initiation and promotion separately in skin carcinogenesis. The results presented here demonstrate that certain congeners of PCBs, PBBs, and TCDD possess the capacity to modify tumor initiation in mouse skin in vivo. At the doses utilized, these chemicals exhibited little or no tumor promoting properties.

Materials and Methods

Animals

Female C3H/HeN mice were purchased from the Charles River Money, Portage, North Wilmington, MA). Mice 6 to 8 weeks old were carefully shaved with electric clippers 2 days prior to treatment and only those mice in the resting phase of the hair were used for the biochemical and tumor experiments. Animals were housed in plastic cages, received water and food *ad libitum*, and were weighed weekly.

Chemicals

DMBA was purchased from Sigma Chemical Company (St. Louis, MO). Benzo[a]pyrene (BaP) was supplied by the NCI Carcinogenesis Research Repository (Bethesda, MD). The phorbol diester promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) was purchased from Dr. P. Herchert, University of Minnesota, Minneapolis, MN. PCB (Aroclor 1254) was purchased from Analabs, Inc. (North Haven, CT). PBB was supplied by A. C. Kolbye, Jr. of the FDA. TCDD (Lot #SI-33) was generously supplied by the Dow Chemical Company (Midland, MI). Purity was [illegible] assay. Spiked samples at 2,7-dichlorodibenzo-*p*-dioxin (DCDD) and 2,3,7,8-tetrachlorodibenzofuran (TCDF) [illegible]

Tumor Initiation Experiments

Each experimental group consisted of 30 pre-shaved mice. DMBA (200 nmol) was dissolved in acetone immediately before use, and 0.2 ml of the acetone solution was applied topically to the shaved dorsal skin of the back. One week after DMBA initiation, control group received application twice weekly of TPA (2.0 μg) in 0.2 ml acetone. The following test compounds: PBB (1000 μg), PCB (1000 μg), and TCDD (10 ng) were applied twice weekly topically in acetone to the shaved dorsal skin area of the DMBA-initiated mice. Promotion was continued for 30 weeks when the experiments were terminated. In another set of similar experiments, animals were pre-treated with PCB (1000 μg) and 6.25 μg) 18 hours prior to initiation. TCDD (10 ng) [illegible]

MONS 207489

[illegible] exposures with TCDD [illegible] of [illegible] [illegible] and TCDD [illegible] [illegible] [illegible]

TABLE 1*

EFFECTS OF PROMOTING AGENTS ON THE INCIDENCE AND NUMBER OF SKIN TUMOR INITIATIONS WITH DMBA†

Treatment‡	Promoter	Dose§	% papillomas per Mouse	Av. papillomas per Mouse
DMBA	None		0	0
None	TPA	10 μg¶	100	3
DMBA	TPA	2 μg	100	9.2
DMBA	PCB	100 μg	0	0
None	PCB	100 μg	0	0
DMBA	PBB	100 μg	0	0
None	PBB	100 μg	0	0
DMBA	TCDD	0.1 μg	0	0
None	TCDD	0.1 μg	0	0

*Diamond, Proc. Soc. Exp. Biol. Med. 149: 428 (1975).
†40 female mice per group promoted for 40 weeks.
‡DMBA was applied in a dose of 200 nmol per mouse.
§Promoters applied once weekly in acetone.
¶TPA applied weekly in acetone.

induction in the mouse, slightly enhanced DMBA initiation at a dose of 10 μg given 3 days prior to initiation.

To further study the inhibitory effects of the dioxins on PAH tumorigenesis, a series of tumor experiments were conducted using DMBA or BaP as initiators. As shown in TABLE 2, pretreatment times of 1, 3 and 5 days (at a dose of 1 μg per mouse) resulted in a 94% inhibition of the tumor response to DMBA. To test the generality of the inhibition, the same experimental design was used with BaP as the initiator. A similar inhibitory action of TCDD on BaP tumor initiation was also observed (unpublished observations). With BaP as the initiator, the dependence on the time of pretreatment with TCDD was similar to that observed with DMBA as the initiator. The maximum

TABLE 2

EFFECTS OF VARIOUS ORGANOHALIDES ON SKIN TUMOR INITIATION BY DMBA
(Pretreated mice were initiated with 2.56 μg of DMBA and promoted with twice weekly applications of 10 μg TPA*)

Experiment	Pretreatment (μg/mouse)	Pretreatment Time	Papillomas per Mouse†	Percent of Control‡
1	Acetone	5 min	3.80	100
2	Aroclor 1254 (100)	5 min	1.60	35
3	Aroclor 1254 (100)	18 hr	2.10	55
4	Aroclor 1254 (100)	3 days	3.90	80
5	Aroclor 1254 (6.25)	18 hr	2.70	71
6	DCDD (100)	3 days	3.44	91
7	TCABDD	3 days	4.71	125
8	TCDBFD	3 days	0.34	9

*40 mice were used per experimental group. Promotion was continued for 20 weeks.
†Average number of papilloma per mouse after 20 weeks of promotion.
‡The average number of papillomas per mouse expressed as a percentage of the DMBA initiated TPA promoted group (experiment 1).

MONS 207491

[illegible] of a similar dose of TCDD with no decrease at 5 days prior to initiation by the inhibitory response to TCDD per se as seen with BaP. Inhibition was less than that observed with DMBA as the initiator. In all cases where the animals received 1 μg of TCDD the weight gain, morphology and histologic characteristics of the skin were normal. At the lowest dose of 3 ng/kg no effect was observed and approximately one third of the mice died at the end of the 20 week period.

To further show that the inhibition of PAH initiation by TCDD was related to the induction of the epidermal monooxygenase system, a dose response study was designed. As illustrated above, maximum inhibition was observed at 3 to 5 days prior to DMBA initiation. As shown in Table 3, TCDD in a dose dependent fashion reduced skin tumor initiation by DMBA. At doses of 0.01 μg, the inhibition of DMBA initiation was approximately 80%, whereas 0.1 μg of TCDD was almost as effective as 1.0 μg. At this writing, these experiments are only in the 15th week and the

Table 3

Effect of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) on Skin Tumor Initiation by DMBA

[Pretreated mice were initiated with 2.5 μg of DMBA and promoted with twice weekly applications of 10 μg of TPA.*]

Experiment	Pretreatment (μg/mouse)	Pretreatment Time	Papillomas per Mouse†	Percent of Control‡
1	Acetone	5 days	3.80	100
2	TCDD (3 ng)	5 days	3.70	97
3	TCDD (0.1 μg)	5 days	0.53	14
4	TCDD (0.3 μg)	5 days	0.32	9
5	TCDD (1.0 μg)	5 days	0.23	6
6	Acetone	5 days	3.81	100
7	TCDD (0.01 μg)	5 days	0.75	33
8	TCDD (0.03 μg)	5 days	0.10	4
9	TCDD (2.0 μg)	5 days	0.02	1

*30 mice were used per experimental group. Promotion was continued for 20 weeks for experiments 1–5 and 15 weeks for experiments 6–9. Promotion is still in progress for both groups of experiments.

†Average number of papillomas per mouse after 15 or 20 weeks of promotion.

‡The average number of papillomas per mouse expressed as a percentage of the DMBA initiated TPA promoted group for each period of promotion (i.e., experiments 1 and 6).

animals have not yet reached plateau tumor levels. The trend is however readily apparent.

Figure 1 shows high pressure liquid chromatographic profiles of metabolites formed upon incubation of 7,12-DMBA with microsomal homogenates from inducer pretreated CD-1 mice. The doses of TCDD and Aroclor 1254 utilized and the pretreatment times were identical to the conditions employed in the tumor experiments in which maximal inhibition of tumor initiation was observed. These high-pressure liquid chromatographic profiles demonstrate that chlorinated hydrocarbons such as Aroclor 1254 and TCDD are capable of inducing epidermal monooxygenases that are responsible for converting DMBA to the formation of hydroxylated products. Furthermore, a good correlation between the increased rates of oxidative metabolism induced by Aroclor 1254 and TCDD and the suppression of DMBA tumor initiation was observed.

MONS 207492

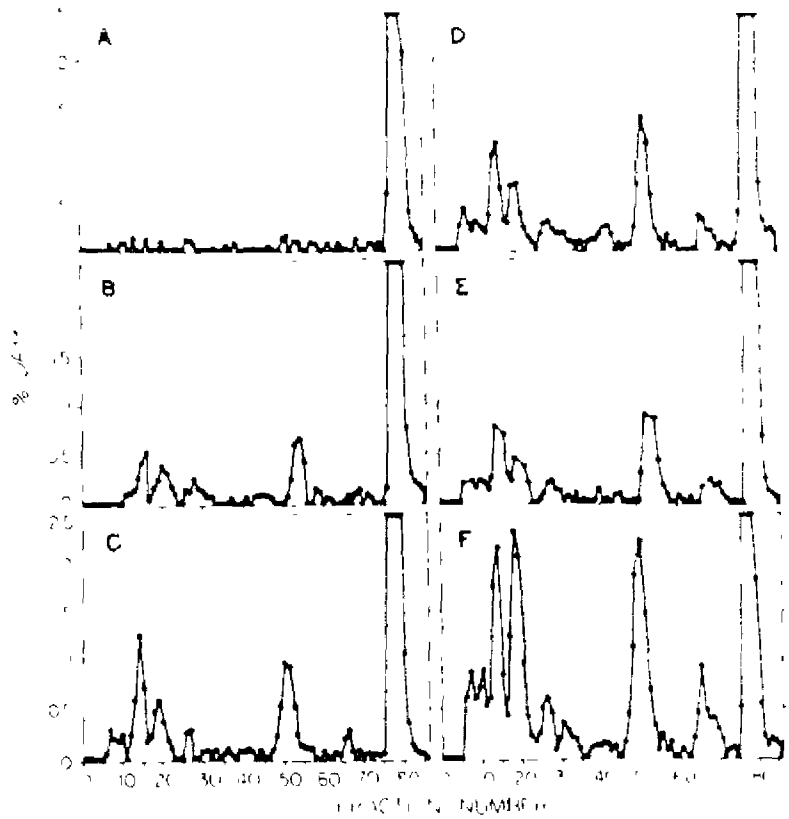
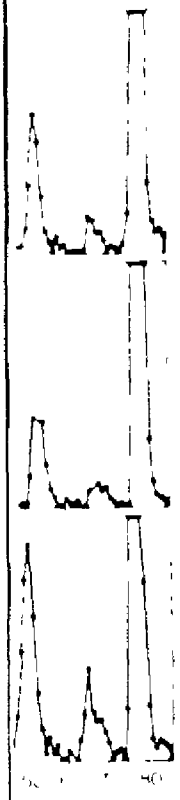


Figure 1. High pressure liquid chromatographic profiles of [illegible] DMBA [illegible] using epidermal homogenate [illegible] *panel B*, DMBA pretreatment (200 mmol/18 hr prior [illegible] *panel C*, 3-methylcholanthrene pretreatment (200 mmol/18 hr prior [illegible] dibenz(a)anthracene pretreatment (200 mmol/18 hr prior to [illegible] 1253 pretreatment (100 μg/18 hr prior to sacrifice) and *panel D*, TCDD [illegible] hr prior to sacrifice). All profiles have been normalized with respect to [illegible] The peak fractions in which various synthetic and rif compounds [illegible] DMBA, 78, 5-hydroxy DMBA, 72, 4-hydroxy DMBA, 70, 2-hydroxy [illegible] DMBA, 61, 12-hydroxymethyl-7-methylbenz(a)anthracene, 57, 7-hydroxymethyl-12-methylbenz(a)anthracene, 52, 5,6-dihydro-5,6-dihydroxy DMBA, 72, 7,12-dihydroxy-[illegible] 39, 8,9-dihydro-8,9-dihydroxy DMBA, 11. Further details of the methodology can be found in reference 77.

To further test the possibility that the effects of TCDD on DMBA-mediated tumor initiation were due to changes in metabolism of the proteinogen, a series of experiments were designed to monitor covalent binding of 11 DMBA to [illegible] DNA, RNA and protein (Exhibit 4). TCDD was applied topically to the shaved back of CD-1 mice (1 μg per mouse) 3 days prior to application of 2.56 μg 11 DMBA [illegible]

MONS 207493



[illegible] DNA, RNA, [illegible] extracted [illegible] method of Hubbard and Sachs.[illegible] TCDD pretreatment reduced the binding of ^{3}H DMBA to DNA at 1 and 24 hours respectively by [illegible] and 72% (Table 4). Similar results were observed with respect to [illegible] binding of ^{3}H DMBA to RNA, although the magnitude was less. However, the binding of ^{3}H DMBA to epidermal protein was not affected by TCDD pretreatment.

Discussion

TCDD and Aroclor [illegible] previously were shown to possess little or no tumor initiating properties [illegible] tumor promoting properties [illegible] mouse skin [illegible] the two stage initiation promotion system of carcinogenesis. Previous studies by Kouri and Van Miller[illegible] indicated that TCDD was carcinogenic in the rat, however, this carcinogenic effect appeared to be related mainly to the promotion of spontaneously occurring tumors. Furthermore, with a hepatic system utilizing an initiation promotion regimen [illegible] PCBs appeared to act as promoters.

This report demonstrates that TCDD possesses remarkable inhibitory action on skin tumor initiation of polycyclic aromatic hydrocarbons (PAH). Almost complete inhibition of DMBA tumor initiation is achieved with a single nontoxic topical dose of 0.1 μg and with a dose of 0.01 μg approximately 80% inhibition was achieved. This potent anticarcinogenic effect may be related to the ability of TCDD to induce epidermal enzyme pathways responsible for detoxifying PAH carcinogens in the skin. Induction of microsomal enzymes in several tissues has been postulated as a mechanism for the anticarcinogenic effects of a wide variety of compounds such as PAH, flavones, coumarins, phenothiazines, and phenobarbital as reviewed by Wattenberg. Induction of microsomal enzyme systems also has been implicated in the anticarcinogenic activity of DDT[illegible] and various polychlorinated biphenyl mixtures. However, investigations such as these have not demonstrated conclusively that the inhibitory actions are a result of induction within the target tissue for a particular carcinogen or that the effect is on tumor initiation *per se*.

The unusually potent inhibitory action of TCDD on skin tumor initiation by PAH described in this report stands in contrast to a report by Kouri, who showed an enhancing effect of TCDD on the formation of 3-MC induced sarcomas at the site of subcutaneous injection. Both compounds were administered simultaneously and the

Table 4

Covalent Binding of ^{3}H DMBA to Mouse Epidermal Macromolecules as Modified by Pretreatment with TCDD

Treatment	Time (Hr)*	Hydrocarbon bound to macromolecule (Pmoles/mg) DNA	RNA	Protein
DMBA	3	48	29	695
DMBA + TCDD†	3	18	16	408
DMBA	24	176	72	388
DMBA + TCDD†	24	35	32	394

*Time of sacrifice after application of ^{3}H DMBA. 40 mice were used for each experimental group.

†Mice in this group received 1 μg of TCDD applied topically 72 hours prior to application of ^{3}H DMBA.

MONS 207494

increased tumor formation is attributed to the ability of TCDD to enhance the retentions of DMBA or vice versa. In view of the time of administration this explanation seems somewhat unlikely. Furthermore, as shown in Table 3, when TCDD was applied 5 minutes prior to initiation with DMBA little or no effect on the tumor response was observed.

The anticarcinogenic effects of TCDD and Aroclor 1254 appear to correlate well with their ability to induce monooxygenase enzymes of the skin. Furthermore, the quantity of [^{3}H]DMBA bound to DNA and RNA (but not protein) in the presence and absence of TCDD-pretreatment correlated well with the tumor response under similar conditions. When taken together these experiments serve to show that pretreatment with TCDD gives rise to an increased rate of inactivation of the DMBA molecule relative to the rate of activation in mouse skin. Although the data point to induction of oxidative biotransformation as a possible mechanism for the inhibitory effects exhibited by TCDD, other mechanisms could be operating. Possibilities include induction in epidermal tissues of nonoxidative metabolic pathways such as epoxide hydratase, glutathione S-transferase, UDP glucuronosyl transferase, or others. Other possibilities include effects on DNA repair systems and on the distribution of the carcinogen to the critical target site(s).

It is deemed possible that future research will enable the development of compounds that evoke minimal toxicity but retain the capacity to inhibit tumor initiation by virtue of their enzyme inducing properties. Of particular advantage would be the production of chemicals capable of selectively inducing various oxacetamide enzymes in particular target tissues. Such chemicals could feasibly serve as important chemopreventive agents in cases in which contact with tumor initiators is necessary or unavoidable.

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MONS 207495

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