# Effects of polyhalodibenzo-p-dioxins on tumor initiation - promotion stages in mouse skin carcinogenesis

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## 1. Introduction

Polyhalogenated aromatic hydrocarbons, of which 2, 3, 7, 8, - tetrachlorodibenzo-p-dioxin (TCDD) has been considered to be toxic, produce a similar pattern of toxicologic effects[1]. TCDD is formed as a trace contaminant in several industrial operations, including paper etc. Life time feeding of TCDD has resulted in an incresed incidence of neoplasms at several organ site[2]. Evidence from experimental and epidermiological studies has demonstrated the multistage step of cancer development. TCDD is effective as a promoting agent during multistage carcinogenesis both in mouse skin and rat liver, and on a molar basis TCDD is hitherto known the most potent animal carcinogens[3,4]. Therefore, it is of interest to investigate the biological activity of various polyhalodibenzo-p-dioxins more extensively. We now report, the effect of tumor initiation and promotion by using the two-stage mouse skin carcinogenesis test system[5].

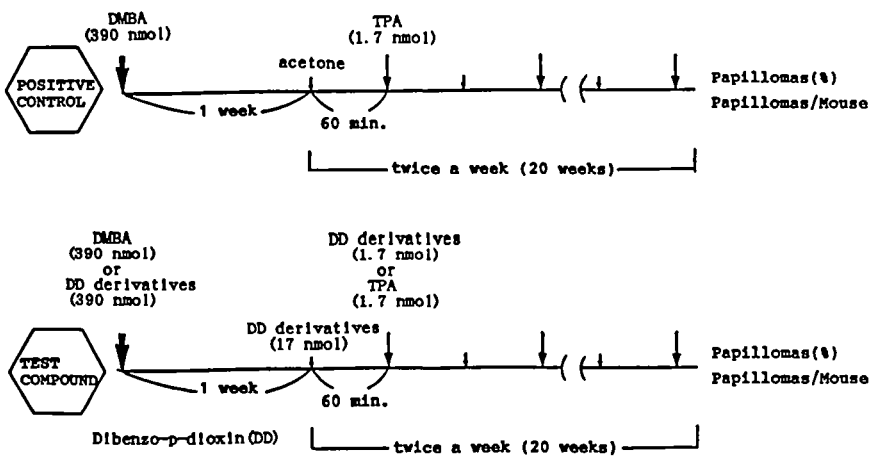
2. Objectives of the study

In laboratory animals and humans, TCDD causes a various pattern of biological- and toxic effects. This compound and related halogenated hydrocarbons are very potent tumor promoters in rodent liver and skin. Many pathological effects of TCDD resemble those of 12-O-tetradecanoylphorbol-13-acetate(TPA). This phenomenon promoted us to examine TCDD as well as TPA regarding. The objective of this study is as followes:i) Evaluation of the tumor initiating and promoting activity of dibenzo-p-dioxin derivatives. ii)Evaluation of the anti-tumor promoting activity of dibenzo-p-dioxin derivatives in two-stage mouse skin carcinogenesis.

3. Approach and Method used

Dibenzo-p-dioxin derivatives were synthesized by one of us (S.U.) from dibenzo-p-dioxin[6)7)]. The tumor initiating, promoting and anti-tumor promoting activity were tested by two-stage mouse skin carcinogenesis (using ICR and SENCAR mouse), as schematically illustrated in Fig 1.

Fig. 1 TWO-STAGE MOUSE SKIN CARCINOGENESIS




i) initiation assay: Dibenzo-p-dioxin derivatives(390 nmol) was applied to the shaved backs of mice. Each mouse was promoted twice a week for 20 weeks with TPA(1.7 nmol) after one week

ii) promotion assay: 7, 12,-Dimethylbenz(a)anthracene (DMBA) (390 nmol) was applied to shave backs of mice. Each mouse was promoted twice a week for 20 weeks with dibenzo-p-dioxin derivatives(1.7 nmol).

iii) anti-promotion assay: DMBA(390 nmol) was applied to shave backs of mice. Each mouse was promoted twice a week for 20 weeks with TPA(1.7 nmol). Dibenzo-p-dioxin derivatives (17 nmol) were applied topically one hour before each TPA treatment.

Control animals(positive control) were treated with DMBA(390 nmol) as an initiator and TPA(1.7 nmol) as a promotor.

4. Result obtained

Data are expressed as 15 mice per group and at the 20th week of treatment

Table 1. Initiating effect of dibenzo-p-dioxin derivative on TPA-induced tumor promotion

| Treatment | 20 weeks | |
|---|---|---|
| | Tumors per mouse | Percentage mice with tumors |
| DMBA + TPA | 9.6 | 100 |
| TBDD + TPA | 3.1 | 100 |

2, 3, 7, 8,-tetrabromo-dibenzo-p-dioxin(TBDD)

Table 2. Promoting effect of dibenzo-p-dioxin derivatives on DMBA-induced tumor initiation

| treatment | 20 weeks | |
|---|---|---|
| | Tumors per mouse | Percentage mice with tumors |
| DMBA + TPA | 9.6 | 100 |
| DMBA + TBDD | 0 | 0 |
| DMBA + OBDD | 0 | 0 |

octabromo-dibenzo-p-dioxin(OBDD)

Table 3. Anti-promoting effect of dibenzo-p-dioxin derivatives on DMBA-TPA induced tumor initiation-promotion

| treatment | 20 weeks | |
|---|---|---|
| | tumors per mouse | Percentage mice with tumors |
| DMBA + acetone + TPA | 9.8 | 100 |
| DMBA + DD + TPA | 3.4 | 73.3 |
| DMBA + TBDD* + TPA | - | - |
| DMBA + OBDD + TPA | 4.0 | 93.3 |
| DMBA + OCDD + TPA | 4.1 | 86.7 |

dibenzo-p-dioxin (DD)

octachloro-dibenzo-p-dioxin (OCDD)

*Animals that died within 10 weeks after TBDD (17 nmol) treatment.

5. Conclusion reached

Mouse skin provides a useful system to study the mechanism of carcinogenesis using tumor initiator and promoter. The studies cited above clearly indicated that dibenzo-p-dioxin derivatives are effective tumor-initiator and anti-promoter of experimental carcinogenesis in mouse skin.

i) We found TBDD that have tumor initiating activity and are 2 to 3 times less sensitive than DMBA initiation by a single application, as shown in Table 1.

ii) The frequency of application of tumor promters is important in the promoting activity. As shown in Table 2, the frequency of application of TBDD and OBDD, even promoting dose of TPA and high promoting dose (data not shown) were ineffective in causing skin tumor.

iii) Some of dibenzo-p-dioxin derivatives listed in Table 3 were shown to inhibit tumor promoting effect induced by TPA. Although the mechanism is not presently understood, they at low dose are a potent inhibitor of tumor promotion.

6. References

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