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Mechanism of Action of Toxic Halogenated Aromatics

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2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and related halogenated aromatic hydrocarbons are a highly toxic class of environmental contaminants, as evidenced by numerous cases of accidental poisonings of human and animal populations and their extreme toxic potency in laboratory animals. The proposed model for the mechanism of action of TCDD and related compounds is analogous to that of the stereoid hormones, which modulate gene expression through a receptor mechanism. In the steroid receptor model, the compound enters the cell cytoplasm where it acts as a specific ligand, binding selectively to a high affinity receptor protein. Bound to the appropriate ligand, the receptor concentrates in the nucleus where its increased association with chromatin leads to altered gene expression. This model has been useful in characterizing the *Ah* receptor; however, it does not provide a unifying hypothesis for all biochemical and toxic effects associated with exposure to halogenated aromatic hydrocarbons. Several findings suggest that a primary factor in determining TCDD toxicity might be tissue and species specific factors that control the actions of *Ah* receptor(s) in target tissues. Furthermore, numerous mechanisms might be involved. Clarifying the mechanism(s) for TCDD toxicity would enhance our ability to predict human health consequences to toxic halogenated aromatic hydrocarbons and would provide a more rational basis for risk analysis.

Introduction

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) has received a great deal of attention in recent years over a growing concern that its presence in the environment may pose a potential human health hazard. This compound and other chlorinated dibenzo-*p*-dioxins, dibenzofurans, azo(xy)benzenes, naphthalenes and biphenyls belong to a class of structurally related chemicals known as the halogenated aromatic hydrocarbons, some of which produce similar patterns of toxicity and biochemical responses and are believed to act through a common mechanism (*1–4*). Many of the halogenated aromatic hydrocarbons are contaminants in commercial products and have become widespread in the environment where their chemical stability, resistance to degradation and lipophilic properties have led to their concentration in the food chain. TCDD is the most potent chemical of this class and is presently one of the most toxic synthetic compounds known (*5*). TCDD is also the most extensively studied of the halogenated aromatic hydrocarbons and has therefore become a prototype for this class of toxic environmental contaminants.

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TCDD can be formed as a by-product in the synthesis of 2,4,5-trichlorophenol from 1,2,4,5-tetrachlorobenzene and therefore may occur as a contaminant of the herbicide 2,4,5-trichlorophenoxyacetic acid and of other products which utilize chlorophenols or chlorobenzenes in their synthesis (*2,6,7*). Chlorinated dioxins have also been discovered in fly ash from municipal and industrial incinerators, an apparent result of incomplete combustion of organic chlorinated compounds (*8,9*).

Several industrial accidents as well as incidents involving improper disposal of waste residues containing TCDD have resulted in accidental poisonings of human and animal populations (*10–14*). Workers involved in the manufacture of 2,4,5-trichlorophenol have experienced a wide variety of health effects including chloracne, hepatic dysfunction, peripheral neuritis, disorders of fat metabolism and porphyria cutanea tarda (*6*). An increased incidence of soft-tissue sarcoma may also occur in these men as well as a group of Swedish men exposed to phenoxy herbicides and chlorophenols during their application (*15,16*). The increasing potential for widespread exposure of man via industrial accidents and careless dumping of chlorinated dioxins has prompted research into their toxicity. Presently researchers are unable to estimate man's relative sensitivity to TCDD and the level of exposure which will produce toxicity.

Toxicity

While investigations with laboratory animals have established TCDD as an extremely potent toxin and teratogen (*5,17*), the mechanism of toxicity has not been determined. In laboratory animals TCDD produces a multitude of toxic responses. The most consistent toxic response to TCDD in all species studied are thymic atrophy and loss in body weight (*18*). The reproductive capabilities of most species is drastically reduced apparently reflecting effects on seminiferous tubules (*19,20*). The hyperplastic responses induced by TCDD exposure predominantly affect epithelial tissues: gastric mucosa (*21,22*), bladder (*23,24*) and skin (*18*), and these responses may be related to a carcinogenic activity of TCDD. Rodent studies implicate TCDD as a potent promoter of rat hepatocellular carcinomas (*25*) and mouse skin tumors (*26*). The wide spectrum of toxic responses to TCDD makes it difficult to specify the organ or the biochemical mechanism responsible for lethality. Tissues can be classified as responding to TCDD in an atrophic or hyperplastic response with the exception of the liver in which both hyperplasia and necrosis are observed. The impact of TCDD exposure on individual organs differs among species and presently cannot be explained (Table 1).

An enigma of TCDD is the tremendous difference in toxicity observed among animal species. The acute LD_{50} of TCDD varies over a 5000-fold range, guinea pig (*5*) being the most sensitive species, followed by rat, monkey, rabbit, mouse, dog, and hamster as the least sensitive species (*27,28*) (Table 1). A similar range (10^3-10^4 difference) in toxicity is observed for such closely related TCDD isomers as 2,3,7,8,- and 1,2,3,8-TCDD (*29,30*) (Table 2). In general, all of the highly toxic halogenated dibenzo-*p*-dioxins show both the same order of species' sensitivity and elicit similar patterns of toxic responses within a given species when administered at a sufficient dose.

An absence of convincing evidence that TCDD is mutagenic (*31*) or that it binds covalently to DNA to any appreciable extent (*32–34*) suggests that TCDD is not an initiator of carcinogenesis and genetic toxicity is not involved in the mechanism of action. There is more supportive evidence, however, that TCDD may act as a tumor promoter (*35,36*). Using a two-stage model of hepatocarcinogenesis, Pitot et al. (*37*), demonstrated that chronic dietary administration of TCDD following a single low dose of diethylnitrosamine resulted in increased enzyme altered foci and hepatocellular carcinomas within 28 weeks. Using this model, TCDD administration resulted in a higher incidence of cancer in a shorter time when compared to chronic feeding studies where carcinomas were observed at 104 weeks in rats and mice (*38*). In the chronic feeding studies it is hypothesized that tumors arise from TCDD promoting action on background initiated cells.

TCDD congeners including 1,2,3,6,7,8-hexachloro- and 1,2,3,7,8,9-hexachlorodibenzodioxin were found to increase the incidence of hepatocellular carcinomas in chronic feeding studies while 2,7-dichlorodibenzodioxin and dibenzodioxin were void of carcinogenic activity in either sex of rats or mice (*39,40*). Hepatocellular carcinoma has also been observed in mice following exposure to the related halogenated aromatics, polybrominated and polychlorinated biphenyls (*41–43*). Like TCDD, polychlorinated biphenyls are tumor promoters in the rat two-stage model of hepatocarcinogenesis (*44*). The mechanism for tumor promoting activity of TCDD and related compounds is unclear, although there is considerable evidence that the toxicity of TCDD and related halogenated aromatics is mediated through the specific binding to a cytosolic receptor. A mechanism of tumor promotion may involve such a cytosolic receptor.

Metabolism

The tremendous variation in species sensitivity to TCDD and related compounds cannot be explained by differences in metabolic rate, clearance times, body burden of the compounds, or by macromolecular adduct formation. TCDD appears to be poorly metabolized as evidenced by whole body half life times of 22–42 days in the guinea pig, 23–31 days in the rat, and 10–12 days in the hamster (*45*). Elimination of TCDD is a first order process in most species. Polar metabolites are formed slowly and excreted in the urine and bile comprising 15% of an administered dose in the rat at 21 days (*46*). The major route of elimination of unmetabolized TCDD is via the feces, which comprises 53% of an administered dose in the rat. In contrast to the general elimination order for most species, the hamster excreted the greatest percentage (41%) of an administered TCDD dose by way of the urine (*47*).

Table 1. Toxic effects of TCDD in various species.[a]

Species	LD^{50}, μg/kg	Liver damage	Weight loss	Chloracne	Thymic atrophy
Guinea pig	0.6–1	–	+	–	+
Monkey	~70	+	+	+ +	+
Rat	25–60	+ +	+	–	+
Rabbit	100	+ +	+	+ +	+
Mouse	200–600	+	+	–	+
Hamster	5500	+	+	–	+

[a]Data summarized from Poland (*27*) and Gasiewicz (*28*).

Table 2. Toxic potency (LD_{50}) of various polychlorinated dibenzodioxins.[a]

	Toxic potency (LD_{50}), μg/kg			
Chlorination	Guinea pig	Rat	Dog	Monkey
2,3,7,8 (TCDD)	–	–	1,000	2
1,2,3,4	–	800	–	–
2,4,8	–	5,000	–	–
2,3,7	29,400	–	–	–
2,8	300,000	–	–	–
1,2,4,7,8	1,125	–	–	–
1,2,3,4,6,7,8,9	–	1,000	–	–

[a]Data from Bickel (*30*).

The primary storage sites for unmetabolized TCDD are the liver and adipose tissue (*46*). Studies with rats, guinea pigs, hamsters, and mice have confirmed liver as the primary site of TCDD distribution with radiolabeled-TCDD levels reaching 50 times that of other tissues (*45*). The *in vivo* hepatic uptake of radiolabeled TCDD was found to be greater in the mouse strain characteristically responsive to TCDD, C57BL/6J, attaining levels twice that of the nonresponsive strain, DBA/2J (*48,49*). However, the whole body half-life was greater in the nonresponsive strain: 24 days compared to 11 days in the responsive strain (*49*). The lipophilicity and low potential for biotransformation of such halogenated aromatic hydrocarbons leads to their distribution and long-term storage in adipose tissue and skin (*50*). TCDD distribution differences were also evident in adipose tissue. The DBA strain attained adipose tissue concentrations twice that of the C57 strain. Differences in pharmacokinetic processes among species may play a role in the biochemical effects of TCDD, however, only a threefold difference in clearance times exist between hamsters and guinea pigs, which is not sufficient to explain the 5000-fold difference in LD_{50} observed between these two species.

Although liver is the primary site of TCDD distribution and accounts for 16-43% of an administered dose, tremendous differences in hepatotoxicity are observed. For example, hepatotoxicity is observed in the guinea pig (*51*) and rat (*52*) following doses of 2 to 400 μg TCDD/kg, while the hamster is resistant, even when hepatic TCDD concentrations are several orders of magnitude greater (*53*). These differences cannot be attributed to metabolic activation of TCDD since virtually all of the radioactivity remaining in the liver in these species is parent compound and extractable (>99%) (*54*).

Enzyme Induction

TCDD is considered a 3-methylcholanthrene (3-MC) -type inducer because of its ability to induce cytochrome P_1-450 and its associated aryl hydrocarbon hydroxylase (AHH) activity (*55,56*) and to suppress such enzymes as benzphetamine *N*-demethylase (*57*) and uroporphyrinogen decarboxylase (*58*). The inductive and suppressive actions of TCDD might be modulated through a cytosolic receptor or by TCDD itself. Suppression of drug-metabolizing enzymes has not been observed in any extrahepatic tissues studied and may be organ specific.

The accumulation of high levels of unmetabolized TCDD in the liver is associated with numerous biochemical and ultrastructural effects, some of which may reflect an adaptive response by the liver such that increasing concentrations of TCDD in the liver induces enzymes which in turn may facilitate its biotransformation and excretion. The proliferation of the hepatic smooth endoplasmic reticulum and induction of several drug metabolizing enzymes, including several forms of cytochrome P450 (*59,60*), UDP-glucuronyltransferase (*61*) and glutathione-S-transferase (*62*) could represent such a response. However, the exact pathways involved in TCDD metabolism have not yet been characterized. In turn, induction of enzymes, such as ornithine decarboxylase by TCDD represent trophic responses and occur during times of hyperplasia (*63*).

The most studied response elicited by TCDD and its congeners is the induction of the hepatic microsomal enzyme aryl hydrocarbon hydroxylase (*56*). Inducibility of cytochrome P_1-450 and its associated AHH activity is genetically regulated by a single locus, the *Ah* locus (*64–67*). Studies based on genetic crosses and back crosses between C57BL/6, the prototype strain responsive to 3-MC induction of cytochrome P_1-450 and AHH activity, and DBA/2, the prototype nonresponsive strain, demonstrated that the *Ah* locus controls expression of a battery of genes, including cytochrome P_1-450, and AHH activity. Essential to the induction process is the existence of a cytosolic *Ah* receptor which binds TCDD and related halogenated aromatics. This receptor appears to control the coordinate expression of the battery of enzymes regulated by the *Ah* locus. To date, TCDD is the most potent ligand for this receptor, being 30,000 × more potent than 3-MC for induction of cytochrome P_1-450 and AHH activity *in vivo* (*68,69*). The lack of sensitivity to AHH inducers observed in the nonresponsive strain has been attributed to a mutation in these mice which produces an Ah receptor with a markedly diminished affinity for AHH-inducing compounds (*68–72*). The capacity of TCDD-receptor interactions to modulate enzyme activity varies with the tissue, as observed by the hyperplastic response in epithelial tissue and atrophic response in thymic tissue. Polymorphism in the *Ah* locus is also observed among animal species. For example, TCDD and 3-MC induce aldehyde dehydrogenase in the rat liver but not mouse. However, both compounds induce hepatic DT-diaphorase in rat and mouse but not guinea pig (*73*).

The results of numerous structure activity studies demonstrate an excellent correlation between the rank order of binding to the cytosolic *Ah* receptor with the induction of AHH and cytochrome P_1-450 in chick embryo liver and rat hepatoma cells (*74–78*), the induction of UDP-glucuronyltransferase, ornithine decarboxylase, DT-diaphorase in mice (*62, 79,80*); ability to produce lethality in guinea pigs, mice, and chick embryos (*81–83*), thymic atrophy and teratogenicity in mice (*56,84,85*), chloracne in hairless mice and rabbits (*86*) as well as keratinization in XB cells (*87*). These studies are important in establishing the relationship between congener structure, receptor binding and toxicity. The induction of several enzymes and toxic responses appear to be mediated through a genetically controlled receptor(s) that exhibits binding affinities dependent on structure of toxic halogenated aromatics. TCDD congeners which are tetra-, penta-, and hexa-isomers halogenated in the 2,3,7,8-positions demonstrate the maximal potency for induction of AHH

activity and toxicity. Structure–activity studies have demonstrated the importance of the 2,3,7,8-positions in induction of AHH in rat hepatoma cells (*88*).

Properties of TCDD Receptor

2,3,7,8-TCDD is presently the most useful ligand for Ah receptor detection and quantitation. The *Ah* receptor is an anomaly in that its structure and mechanism is analogous to known steroid receptors; however, no known steroid or endogenous compound is a ligand for the receptor. The Ah receptor is present in the cytosol with the liver and lung containing the highest proportion of receptor in guinea pig, hamster, rat, and mouse (*29,89*) (Table 3). High levels of receptor exist in thymic tissue of guinea pig and rat. Low levels were detected in mice and hamster. Most other tissues examined contain low or undetectable levels of receptor except for guinea pig testes, which exhibited levels comparable to liver values. Variations in receptor numbers and affinity for ligand may play a role in the pleiotropic sensitivity of the tissue and species. For example, the sensitivity to thymic atrophy in the rat and guinea pig may be explained by the existence of receptor levels eight times those observed in the less sensitive mouse or hamster (*53,90*).

The *Ah* receptor has been most notably characterized in hepatic tissues. Literature values for hepatic receptor concentrations of guinea pig, rat, monkey, mouse and hamster range from 23 to 74 fmole/mg cytosolic protein and exhibit a reversible high affinity binding for TCDD, K_d 0.1 to 0.4 nM (*28*). This binding is competed for by 2,3,7,8-tetrachlorodibenzofuran, 3-methylcholanthrene, benzo(a)pyrene and β-naphthoflavone—all inducers of AHH activity—and is not competed for by inducers of other forms of cytochrome P-450 such as phenobarbital or 16α-cyanopregnenolone (*91*), or the steroids, dexamethasone, progesterone, estradiol, testosterone, and 2-hydroxyestradiol (*75*). Qualitatively, the hepatic cytosolic *Ah* receptor has markedly similar properties among the species examined. The receptor displays a 5S sedimentation coefficient on sucrose density gradients, a stokes radius of 6.6 nm and a molecular weight of 136,000 in rat liver cytosol. The receptor is heat labile and inactivated by trypsin (*92*).

The ontogeny of the *Ah* receptor has been studied in hepatic tissues of rat, mouse, and rabbit (*93,94*). Receptor levels increased postpartum, reaching maximum levels by 21 days and declining through adulthood. Peak receptor levels at 21 days corresponded with maximal AHH induction. Receptor levels in the lung paralled the postpartum increase seen in the liver with maximum levels exhibited at day 15. In the thymus, receptor levels remained relatively constant throughout the 42 day study with levels attaining half the maximum levels observed in the liver and lung. Hepatic receptor concentrations are not significantly altered by orchiectomy, ovariectomy, adrenalectomy or, hypophysectomy (*95*).

Several studies have attempted to investigate nuclear uptake and binding of TCDD and related halogens and the role that cytosolic and/or nuclear receptors play in this process. There are some indications that the *Ah* receptor is primarily nuclear (*96*), and the cytosolic receptor represents, in part, artifacts arising during subcellular fractionation. Nevertheless, the nuclear translocation process may be important.

The intranuclear binding of TCDD has been detected in the liver, lung, thymus, and kidney of C57BL/6J and DBA/2J mice (*97,98*) Sprague-Dawley rats (*98,99*) and cultured hepatoma cells (*100*). Translocation of the *Ah* receptor from the cytoplasm is neither temperature-sensitive nor does it require an activation step, in contrast to known steroid receptor systems (*101*). Following injection of rats with radiolabeled TCDD, maximum nuclear uptake was observed simultaneously with a decline in cytosolic radioactivity at 2 hr in the liver and 3 hr in thymus (*99,102*). TCDD does not bind DNA unless it is bound to receptor and the inductive/repressed cellular responses appear to require nuclear binding (*97,101*). The nuclear binding component is similar to the cytoplasmic entity in that it is saturable, heat labile, sensitive to proteolysis, displays an equilibrium dissociation constant of 1.05 nm and sediments in the 4 to 5S region on sucrose density gradients (*102*). Nuclear *Ah* receptor concentrations range from 8 to 16 fmole/mg nuclear protein for liver, lung and kidney in the C57BL/6J mice and Sprague-Dawley rats. Following equivalent doses of TCDD, nuclear Ah receptor concentrations for liver, lung and kidney in the non-responsive DBA/2J mice were two- to three-fold lower than those in the responsive C57BL/6J strain (*98*).

Table 3. Concentrations and dissociation constants (K_d) of cytosolic receptor from various species and tissues.[a]

	Liver		Thymus	
Species	Concn, fmole/mg protein	K_d, nM	Concn, fmole/mg protein	K_d, nM
Guinea pig	59 ± 11	0.06 ± 0.01	47 ± 7	0.10 ± 0.07
Rat	61 ± 23	0.12 ± 0.03	138 ± 15	0.12 ± 0.05
Mouse				
C57BL/6J	74 ± 10	0.29 ± 0.01	24 ± 2	0.27 ± 0.03
B6DZF1/J	23 ± 2	0.42 ± 0.03	9	0.35
DBA/2J	ND	ND	ND	ND
Hamster	67 ± 22	0.33 ± 0.07	5 ± 6	0.24 ± 0.08

[a]Data summarized from Gasiewicz (*28*).

TCDD is the only known ligand capable of triggering translocation of the "defective" *Ah* receptor in DBA/2J mice and which is sufficient to evoke a response, induction of cytochrome P_1-450. Translocation of the TCDD-receptor complex from the cytoplasm to the nucleus may vary with the tissue. For example the liver and thymus contain equivalent amounts of cytoplasmic receptor, but nuclear uptake by the thymus of TCDD-receptor complexes following *in vivo* exposure is only 6% of that observed in the liver (*99*).

Despite large differences in species toxicity and an inability to relate tissue *Ah* receptor levels to toxicity, all species examined possess marked similarities in the receptor properties, tissue distribution and ontogeny of the *Ah* receptor. The functional aspect of this receptor, the reason for its conservation among species and the properties and function of a possible endogenous ligand are as yet unknown. The functional capacity, however, of the *Ah* receptor is dramatically different when comparing the liver and thymus. Following exposure to TCDD, the liver displays primarily a hyperplastic response while an atropic response is exhibited by the thymus. Factors such as receptor subpopulations, translocation and receptor binding to DNA may influence the differential expression of various gene products. Cytoplasmic *Ah* receptor levels of relative binding affinities are similar for the liver and thymus. However, the quantity of receptor translocated to the nucleus following TCDD challenge is several fold greater in the liver than thymus although possible tissue differences in DNA binding sites have not been investigated.

The binding affinity and concentration of hepatic cytosolic receptor are similar for guinea pig, rat, C57B mice, rabbit and hamster, yet there exists a 5000-fold difference in LD_{50} values for TCDD between guinea pig and hamster. Comparisons of cytosolic liver receptor concentrations may not be an adequate indicator of potential TCDD toxicity but rather nuclear TCDD receptor interactions may explain the mechanism of TCDD toxicity.

Summary and Conclusion

The proposed model for the mechanism of action of TCDD and related compounds was derived from models for steroid-hormone receptors (Fig. 1). TCDD enters the cell and binds with high affinity to the *Ah* receptor(s) in the cytoplasm. This receptor is selective for TCDD and related compounds; i.e., it does not bind steroid hormones or other compounds that do not produce the spectrum of biochemical and histopathological effects characteristic of TCDD exposure. The *Ah* receptor has a finite capacity (fmole/mg cytosol protein) which leads to saturation at low concentrations of ligand allowing maximal responses at low doses. It is thought that the TCDD receptor complex translocates to the nucleus where it binds to specific sites on chromatin thereby modulating gene expression producing induction and/or repression of synthesis of critical macromolecules.

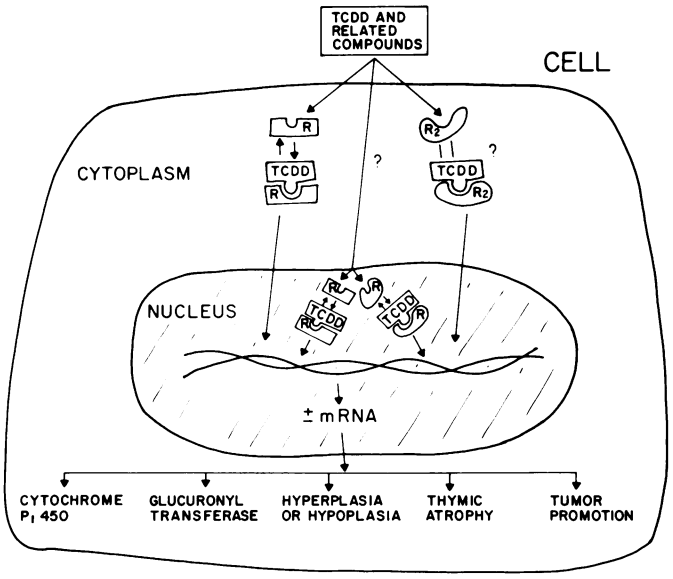

FIGURE 1. Model for mechanism of action of TCDD and related compounds.

However, little is known about the nuclear translocation and binding process.

This model is attractive in its simplicity but unfortunately it does not provide a unifying hypothesis for all biochemical and toxic effects associated with exposure to TCDD. For example, there are huge species variations in susceptibility to hepatic enzyme induction, lethality and histopathologic effects in spite of the presence and similarity of properties of receptor in these species. In other words, the correlations that exist between cytosolic receptor concentrations and toxicity in inbred strains of mice are not present in other species. Moreover, species differences in metabolic and clearance rates are relatively small and cannot account for species variations to toxicity. These findings suggest that a primary factor in determining toxicity might be tissue and species specific factors that control the actions of receptor in target tissues. There are numerous possible mechanisms that might be involved. For example, a critical step in receptor action might be nuclear translocation rates, the location of binding sites for the TCDD-receptor complex on DNA, or tissue and species specific control over the biochemical events that control gene expression following nuclear binding. Alternatively, there may be more than one receptor, each producing different effects or competition of TCDD with a possible endogenous ligand and may be important. Clarifying the mechanism(s) for TCDD toxicity would enhance our ability to predict human health consequences to toxic halogenated aromatics and help determine whether the human is a "sensitive" or "resistant" species. Such information would provide a more rational basis for risk analysis. For example, if nuclear occupancy of receptor is the critical or rate-limiting step, then measurement of TCDD-receptor complexes in the nucleus would represent the "biologi-

cally-effective dose." This parameter, coupled with exposure data and toxicity evaluation, would tell us the dose of TCDD required to estimate a specified risk to effects such as tumor promotion.

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