NTP Research Concept: Phenolic Benzotriazoles

Project Leader

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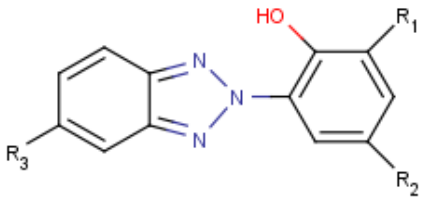
Background and Rationale



The Phenolic Benzotriazoles (PBZTs) class was nominated to the NTP testing program by the NIEHS.

These chemicals are used as UV stabilizers within products to increase stability to light. As industrial additives, they are used in paints, rubber, plastic, and electronic products. Some PBZTs are used in food contact polymers and adhesives, cosmetics, sunscreens, and fragrances. Generally speaking, the class is made up of chemicals with single substitutions on the phenolic ring (R2), double substitutions on the phenolic ring, double substitutions on the phenolic ring that includes an ester bond, and a collection of other PBZTs with various substitutions (multiphenolic rings, an octrizole dimer (bisoctrizole), etc.). A few PBZTs have chlorine substitutions at the R3 position. Production of these chemicals ranges from unknown production up to ten million pounds per year. Twenty nine chemicals have been identified in this class, but this concept will focus primarily on the ten PBZTs with production values reported under the latest US Environmental Protection Agency's Inventory Update Rule (IUR) (table below).

Name	CAS	2006 IUR (lbs)
Octrizole	3147-75-9	1 to < 10 million
DitPe-BZT	25973-55-1	1 to < 10 million
DiMeEtPh-BZT	70321-86-7	1 to < 10 million
tBuPrMeEst-BZT	84268-33-7	1 to < 10 million
tBu(C7-9)Est-BZT	127519-17-9	1 to < 10 million
Drometrizole	2440-22-4	500k to < 1 million
Bumetrizole	3896-11-5	500k to < 1 million
MeEtPhMeBu-BZT	73936-91-1	500k to < 1 million
DBHCB	3864-99-1	< 500k
Bisoctrizole	103597-45-1	< 500k

The potential lipid solubility (high log K_{ow}) for most of these PBZTs suggests that they may have bioaccumulative potential and environmental predictions suggest that they may have half-lives of six months to a year in the environment. Studies have identified several of these chemicals within marine wildlife, soil/sediments, and seafood (*1-4*). Exposure likely occurs through an oral route from environmental contamination. However, there will be dermal exposure to PBZTs used in cosmetics (e.g. octrizole,

drometrizole, and bisoctrizole (bisoctrizole is used in products outside of the US)). Human exposure data (i.e., plasma levels) are not known.

Toxicity data for chemicals within this class varies. Seven PZBTs were negative when tested for genotoxocity *in vitro*. Drometrizole has the most complete set of toxicity studies, with a subchronic, prenatal, and chronic study. Based on study summaries, the drometrizole chronic study did not identify a toxicity in mice, identified weight loss at the high dose in rats, and there was no increase in the incidence of neoplasms in either species. Other PhBTs, such as tBuPrMeEst-BZT (CAS# 84268-33-7) and tBu(C7-9)Est-BZT (CAS# 127519-17-9), do not have an identified toxicity study. Overall in the reported subchronic studies, the liver and kidneys are fairly consistent target organs. The male and female reproductive tracts were also targets for selected PBZTs. There have not been any comprehensive reproductive studies identified for this class with only a dominant lethal study to evaluate male germ cell toxicity (drometrizole), and a screening reproductive study (OECD 421) for DBHCB. Drometrizole was reported negative for prenatal toxicity, and DiMeEtPh-BZT (CAS# 70321-86-7) reduced fetal weights and delayed skeletal maturation at the mid-dose in the absence of maternal toxicity.

Estrogenic and androgen receptor activity has been evaluated for some PBZTs and studies report no activity (*5, 6*). There is a sex difference in toxicity response for some PBZTs. Male rats are more sensitive than females after exposure to 2-(2′-hydroxy-3′,5′-di-*tert*-butylphenyl) benzotriazole (HDBB) or DBHCB. This sex specific sensitivity is not present in pre-pubertal animals and can be abrogated by castration (*7, 8*). However, kinetics between adult male and female rats was not found to be different for HDBB, but toxicodynamic differences in the liver may exist (*9*). The half-life of tBuPrMeEst-BZT (CAS# 84268-33-7) in rats was found to be 12 hrs (*10*).

Dermal toxicity and sensitivity has been evaluated for drometrizole. In a murine local lymph node assay and guinea pig maximization test, drometrizole was classified as a non-sensitizer. Benzotriazole, lacking the phenolic substitution, was classified as a non-sensitizer in a guinea pig maximization test. Octrizole was negative in a repeat patch test in human. An acute dermal toxicity evaluation was negative for DiMeEtPh-BZT (CAS# 70321-86-7).

Key Issue

Identifying which chemicals in the PBZT class should undergo toxicity evaluation and what types of toxicity evaluation will be a challenge to moving forward. Ideally, instead of testing all chemicals within the class, specific chemicals with the highest potential for hazard and/or internal exposure would be evaluated. Furthermore, identifying specific potential toxicities (e.g., reproductive) and tailoring further testing to these toxicities would allow a more targeted approach to a class evaluation.

Specific Aims

1. Evaluate the PBZTs class in short-term *in vitro* and/or *in vivo* assays to prioritize chemicals on the basis of potential toxicity and accumulation potential

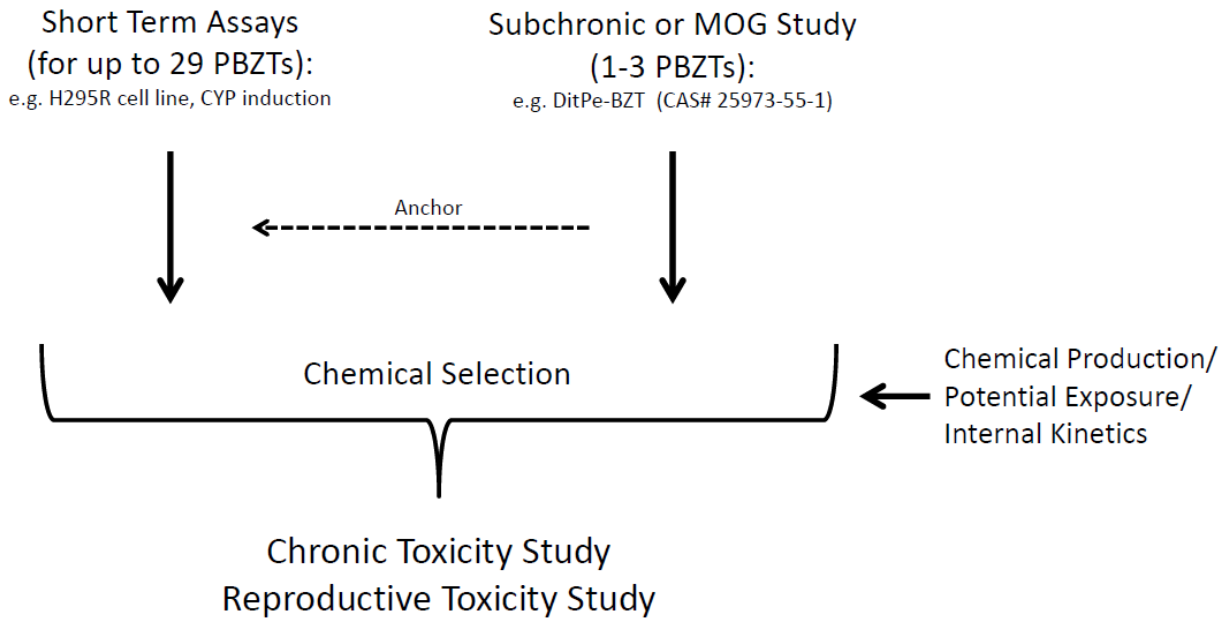
2. Selected chemicals will undergo toxicity evaluation, which may include reproductive, prenatal, and subchronic toxicity evaluations in order to anchor the short term assays

3. Evaluate the ADME and TK of selected PBZTs via oral and potentially dermal routes of exposure and between males and females to better understand the influence of route of exposure and sex on internal dose

4. A chronic toxicity study may be warranted based on extensive exposure and limited chronic toxicity evaluation for the class

Proposed Approach

The PBZT class will be evaluated using short term *in vitro* studies, and possibly short term *in vivo* studies, in order to prioritize chemicals for further testing. The use of *in vitro* methods will allow for a first pass evaluation of the chemicals (up to twenty nine) within this class. These chemicals may be enzyme inhibitors similar to other triazole and imidazole compounds, thus short-term studies will likely take a targeted approach to evaluating cytochrome P450 induction, steroid synthesis inhibition, and metabolism. High throughput screening for assessing the activities of this class would be problematic due to the high log P they display. Chemicals with a high potential for toxicity or high potential for internal accumulation may be further tested in appropriate *in vivo* toxicity tests.



In parallel to the short term assays, selected PBZTs will be evaluated for developmental and/or subchronic toxicity, which will help anchor the data set that is generated from short term studies and provide data for risk assessment (Figure above). Decisions to test PBZTs further would be based on exposure, production, differences in structure, and/or potential for toxicity. DitPe-BZT (CAS# 25973-55-1), a PBZT with dual substitutions on the phenolic ring, will be evaluated since it has been identified in the environment, has a high production volume, a log K_{ow} of 7.3, and indications of reproductive toxicity. These considerations make it ideal for testing in the modified one-generational (MOG) study which can incorporate a subchronic and reproductive toxicity evaluation. Evaluation of other PBZTs is tentative and could be influenced by the information gathered from the short term studies, structure, and/or additional exposure information. Octrizole, a high production volume and single substituted phenolic ring PBZT, with only a thirty-day toxicity test in rats could be evaluated. This chemical is used in cosmetics, so dermal exposure studies, possibly including photo-toxicity tests, would be considered. The PBZT tBu(C7-9)Est-BZT (CAS# 127519-17-9), another PBZT with a high production volume and dual substitutions, but with an ester linkage and no identified toxicity data, could be tested in likely a subchronic or MOG study. If PBZTs with varying structures (single substitution, double substitution, etc.) are tested, then these data would aid in toxicity evaluation of the class.

Based on previous assays, PBZTs do not appear to be sensitizers, but sensitization tests may be included if a specific PBZT is determined to have extensive dermal exposure. Selected chemicals would also undergo evaluation for toxicokinetic and ADME properties, since very little work has been conducted to determine properties such as half-life for chemicals in the class. Chronic studies will be considered based upon exposure data, and potential of hazard based upon the prioritization studies and longer term *in vivo* studies. The logistics and priority for generating PBZT human exposure data will be discussed with Federal partners.

Significance and Expected Outcome

The presence of this class of chemicals in the environment, with the potential of accumulation, and some use in cosmetics and sunscreens, requires a better understanding of the hazards associated with PBZTs. Some chemicals within this class are produced at a high production volume and collectively there is a high potential for exposure to one or several PBZTs. A class evaluation that incorporates a prioritization or ranking of hazard concerns in combination with anchoring to *in vivo* evaluations would aid in the risk assessment of PBZTs. The identification of PBZTs with a hazard concern and evaluation of toxicokinetic parameters will also provide a basis for selecting chemicals for specific applications.

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