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## BENZOTHAZOLE TOXICITY ASSESSMENT IN SUPPORT OF SYNTHETIC TURF FIELD HUMAN HEALTH RISK ASSESSMENT

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Synthetic turf fields cushioned with crumb rubber may be a source of chemical exposure to those playing on the fields. Benzothiazole (BZT) may volatilize from crumb rubber and result in inhalation exposure. Benzothiazole has been the primary rubber-related chemical found in synthetic turf studies. However, risks associated with BZT have not been thoroughly assessed, primarily because of gaps in the database. This assessment provides toxicity information for a human health risk assessment involving BZT detected at five fields in Connecticut. BZT exerts acute toxicity and is a respiratory irritant and dermal sensitizer. In a genetic toxicity assay BZT was positive in *Salmonella* in the presence of metabolic activation. BZT metabolism involves ring-opening and formation of aromatic hydroxylamines, metabolites with mutagenic and carcinogenic potential. A structural analogue 2-mercaptobenzothiazole (2-MBZT) was more widely tested and so is used as a surrogate for some endpoints. 2-MBZT is a rodent carcinogen with rubber industry data supporting an association with human bladder cancer. The following BZT toxicity values were derived: (1) acute air target of 110  $\mu\text{g}/\text{m}^3$  based upon a BZT  $\text{RD}_{50}$  study in mice relative to results for formaldehyde; (2) a chronic noncancer target of 18  $\mu\text{g}/\text{m}^3$  based upon the no-observed-adverse-effect level (NOAEL) in a subchronic dietary study in rats, dose route extrapolation, and uncertainty factors that combine to 1000; (3) a cancer unit risk of  $1.8\text{E}-07/\mu\text{g}\cdot\text{m}^3$  based upon a published oral slope factor for 2-MBZT and dose-route extrapolation. While there are numerous uncertainties in the BZT toxicology database, this assessment enables BZT to be quantitatively assessed in risk assessments involving synthetic turf fields. However, this is only a screening-level assessment, and research that better defines BZT potency is needed.

Synthetic turf fields that are cushioned by a layer of crumb rubber in between the blades of synthetic grass possess the potential to release rubber-related compounds such as polycyclic aromatic hydrocarbons (PAH), nitrosamines, zinc (Zn), and benzothiazole (BZT). Benzothiazole itself is commonly present in rubber and has sufficient volatility to be a source of inhalation exposure to those playing on synthetic turf fields. Recent investigations in Connecticut and elsewhere identified BZT

as the major rubber-related chemical detected in laboratory off-gas studies as well as in investigations of synthetic turf fields (Simcox et al. 2011; Li et al. 2010; NILU 2006; NYSDEC 2009). However, the potential health risks associated with BZT detections at artificial turf fields have not been extensively examined, in part due to a limited toxicology database.

The goal of this study was to assess BZT toxicity in support of a risk assessment of synthetic

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This article and underlying risk assessment report were reviewed by staff from the Connecticut Department of Public Health. The Connecticut Academy of Science and Engineering reviewed the underlying report and made formal recommendations (CASE June 15, 2010, report) that are reflected in this article.

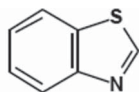
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turf fields conducted by the Connecticut Dept of Public Health (Ginsberg et al. 2011). There was a reliance upon the limited BZT database as well as data for surrogate chemicals in order to develop toxicity values for the acute, chronic, and carcinogenic potency of BZT. This information may have applicability to other assessments involving BZT.

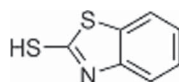
### PROPERTIES AND USES

BTZ is a clear yellow liquid with a sulfur or rubbery odor (Lewis 1993). The heterocyclic structure provides multiple functionality and opportunities for derivatization, making it a good starting material for other industrial chemicals. BZT is a precursor for rubber accelerators, a component of cyanine dyes, as slimeicides in the paper and pulp industry, and used in the production of certain fungicides, herbicides, antifungal agents, and pharmaceuticals (Bellavia et al. 2000; Seo et al. 2007). BZT imparts a meaty, nutty, or coffee taste and thus is used in various foods as a flavoring agent at levels up to 0.5 ppm (NTP 1997). BZT has limited solubility in water (4.3 g/L at 25°C) and relatively low volatility (vapor pressure 0.014 mm Hg at 25°C).

The toxicology database for BTZ is limited to short-term, subacute, and mutagenicity studies. A related chemical, 2-mercaptobenzothiazole (2MBZT), has been subjected to more extensive testing and thus used as a surrogate for some endpoints. The structures are presented here:



Benzothiazole: CAS number 95-16-9



2-Mercaptobenzothiazole; CAS number 149-30

### EXPOSURE TO BZT

The most common exposure is ingestion of foods, beverages, and pharmaceuticals that contain BZT. Inhalation is also common as this chemical is present in tobacco smoke and may be in the atmosphere from the wearing down of tires. Atmospheric forms include both the particle-bound and gaseous states. Workers in rubber processing facilities are particularly likely to receive inhalation and dermal exposure. The amount of background exposure to the general public in the diet or general environment has not been calculated and BZT does not appear to have been the subject of human biomonitoring studies. In addition, there are very few environmental measurements. BZT was detected in relation to artificial turf fields in several previous studies. A concentration of 6.5  $\mu\text{g}/\text{m}^3$  was found in 1 air sample taken at the surface of an artificial turf field in New York City under summertime conditions in full sun. BZT was not detected at this field at the 3-ft height or at the surface of another field tested under similar conditions (NYSDEC 2009). A Norwegian study (NILU 2006) detected 3.4–31.7  $\mu\text{g}/\text{m}^3$  in its air samples at indoor artificial turf fields. In addition, the Connecticut Agricultural Experiment Station (Li 2010) conducted headspace analyses of crumb rubber at elevated temperature (60°C) in which it found BZT at 226 ng/ml, which was greater than the other detected analytes. Thus, in spite of its limited volatility, BZT has the potential to off-gas from crumb rubber used in artificial turf fields and present as the major rubber-specific component.

Rubber is also used as a cushioning agent in flooring, carpet backing and playscapes leading to the potential for BZT exposure in indoor and outdoor environments. Data are not available for BZT measurements in relation to these uses.

### TOXICOKINETICS OF BZT AND 2MBZT

Both BZT and 2MBT are well absorbed and rapidly excreted, with metabolites appearing primarily in urine and small amounts in

feces. Evaluation of BZT metabolism and elimination is limited to one study in guinea pigs that identified metabolites in urine after ip administration of 30 mg/kg daily for 4 d (Wilson et al. 1991). Urinary metabolites consisted of the heterocyclic ring scission products 2-methylmercaptoaniline, 2-methylsulfanylamine, 2-methylsulfonylaniline, 2-methylsulfanylphenylhydroxylamine, and 2-methylsulfonylphenylhydroxylamine. These BZT metabolites are reactive, particularly with respect to the free amine and the aromatic hydroxylamine (NHOH) group present in several metabolites. Sulfate and glucuronide conjugates of these metabolites were also recovered in the guinea pig study. In contrast to BZT, 2-MBZT undergoes metabolism primarily via conjugation of the sulfhydryl moiety at the 2- position. This leads to a variety of 2'-glucuronide and sulfate benzothiazole metabolites (El Dareer et al. 1989; Fukuoka and Tanaka 1987; Fukuoka et al. 1995). Thus, instead of ring scission, 2MBT undergoes conjugation of the side chain functional group, leaving the ring structure intact.

### TOXICITY OF BZT INCLUDING RELEVANT DATA FROM 2MBT

#### Acute Toxicity

A variety of acute studies in animals demonstrated a degree of acute toxicity for BZT. The median oral lethal dose (LD<sub>50</sub>) is between 380 and 900 mg/kg. Intravenous, intraperitoneal, and dermal LD<sub>50</sub>s are lower, ranging from 95 to 200 mg/kg. The acute toxicity of BZT is characterized by CNS and respiratory depression as well as liver and kidney toxicity (Bogert and Husted 1931; Zapór 2005). A repeat dose study in mice receiving 110 mg/kg injections for a week noted liver necrosis and cloudy swelling of the renal tubules (Guess and O'Leary 1969). Higher doses resulted in peripheral vasodilation, extensive salivation, and convulsions. 2MBZT acute toxicity studies demonstrated variable results with the oral LD<sub>50</sub> in rats ranging from 100 to 7500 mg/kg. Since most of the reported LD<sub>50</sub>s are over

1000 mg/kg, 2MBZT appears to be somewhat less acutely toxic than BZT.

BZT appears to be a skin allergen as positive dermatitis reactions occurred in 17 of 43 human subjects treated topically (Bogert and Husted 1931). The dermatitis was often delayed in appearance and after fading would reoccur on the initial site if BZT were reapplied to a different site. Similarly, 2MBT has demonstrated contact dermatitis and sensitization in humans and rodents (Wang and Suskind 1988; Ikarashi et al. 1993).

BZT may be a nose and throat irritant, based upon anecdotal reports of greater irritation of asphalt-rubber workers laying pavement than when nonrubber products are used for this purpose. The greater irritation was attributed to the presence of BZT, but other rubber ingredients may have contributed to the effect, especially at the high temperatures used to surface roads (Bustnes et al. 2007).

A study by the U.S. Consumer Product Safety Commission (CPCS 1996) tested the sensory and pulmonary irritation of various compounds in carpet, one of them being BZT. Mice were exposed to 60 min of control or contaminated air and sensory irritation indicated by a decline in breathing rate. The concentration that produced a 50% decrease in respiratory rate (RD<sub>50</sub>) for BZT was 235.4 mg/m<sup>3</sup>. The positive control in this test was formaldehyde, which had an RD<sub>50</sub> of 12.9 mg/m<sup>3</sup>. This study provides an indication of BZT irritating potency to the respiratory tract relative to the known irritant formaldehyde (18 fold less potent).

#### Mutagenicity

The only study of BZT mutagenicity was in *Salmonella typhimurium*, in which a mutagenic response was detected in strain TA1537 in the presence of a metabolic activation (S9) system (Kinae et al. 1981). 2MBZT was evaluated more extensively with negative results in four different tests involving *Salmonella* with and without metabolic activation; none of the *Salmonella* strains showed evidence of mutagenesis (Whittaker et al. 2004). However, it was

mutagenic in two different mouse lymphoma assays with metabolic activation and it was a clastogen in the Chinese hamster ovary chromosomal aberration assay. This *in vitro* finding of clastogenicity did not transfer to *in vivo*, as the mouse micronucleus test was negative in two different mouse strains (Whittaker et al. 2004).

### Subchronic and Chronic Toxicity and Cancer

There are no subchronic or chronic studies for BZT in the published literature or governmental reports. However, an unpublished 90-d dietary study conducted in 1971 was submitted by the Flavor and Extract Manufacturers' Association to the World Health Organization (WHO). WHO (2003) cites this study (Morgareide 1971) as providing evidence that groups of 15 FDRL rats/gender were dosed in their diet with BZT at 5.1 mg/kg/d. Animals were observed for clinical signs of toxicity, and at 6 and 12 wk blood was taken for standard hematology and clinical chemistry parameters. Histopathology was performed at study termination. Further methodological details are not available. WHO (2003) reported that the test diet was well tolerated with no alterations in blood parameters, organ weights, or histopathology due to this level of BZT. Therefore, the oral dose of 5.1 mg/kg/d was considered a NOAEL. As described below, this NOAEL was used by New York State to develop an inhalation toxicity value for BZT of 18  $\mu\text{g}/\text{m}^3$  in their 2009 risk assessment.

2MBZT has been more thoroughly tested, with its database covering 90-d and 2-yr studies in rats and mice by the oral (gavage in corn oil vehicle) dose route (NTP 1988). The most sensitive effect in the 90-d studies was hepatomegaly in the livers of male rats seen at the lowest dose (188 mg/kg/d) and higher. A 20-mo dietary study in mice found 2MBZT associated with microscopic changes in the kidney at a dose of 58 mg/kg/d and higher with the NOAEL reported to be 14 mg/kg/d (Whittaker et al. 2004).

BZT has not been subjected to cancer bioassay testing but has been listed as a high priority for such testing by the National Toxicology Program (NTP 1997). However, this ranking has yet to be followed up with actual testing. The high ranking appears to stem from the potential for widespread exposure in food and certain occupations, as well as the single positive mutagenicity test (Kinae et al. 1981). 2MBZT has been fully tested by NTP for carcinogenic potential in 2-yr rat and mouse studies (NTP 1988). Gavage doses of 188 or 375 mg/kg/d, 5 d/wk, in female rats or 375 or 750 mg/kg/d in male rats yielded a variety of compound-related tumors, including tumors of the adrenal gland (both genders), pituitary gland (both genders), pancreas, and preputial gland, and leukemia (males only). Further, male rats had a low incidence at both doses of renal transitional-cell tumors that appear to be compound related, due to the fact that these tumors are rare in the controls. In mice dosed by gavage with 375 or 750 mg/kg/d, the only positive response was in female liver and this was only at the low dose.

The carcinogenicity of 2MBZT was evaluated in several epidemiological studies involving workplace exposure. Bladder cancer excess was seen in studies of the rubber industry in relation to worker exposure to vulcanization inhibitors, accelerators, antioxidants, and other specialty chemicals (Sorahan 2008). A chemical factory in North Wales has been a particular focus because it produces chemicals for the rubber industry. Departments working with aromatic amines (aniline, *o*-toluidine, phenyl-beta-naphthylamine) and 2MBZT were the main focus, with excess bladder cancer risk seen for *o*-toluidine and 2MBZT exposure (Sorahan 2008). A follow-up study of 363 of these 2MBZT-exposed workers found higher bladder cancer mortality (SMR = 3.74, range 1.6–7.4) relative to national rates for this gender and age group. 2MBZT exposure was also associated with intestinal cancer and multiple myeloma in these workers (Sorahan 2009). A study of 600 West Virginia rubber chemical workers with exposure to 2MBZT found a significant increase in bladder cancer

mortality for workers exposed to both 2MBZT and 4-aminobiphenyl (SMR = 27.1, 95% CI 11.7–53.4) but not to 2MBZT alone (Collins et al. 1999). This suggests an interactive effect with aromatic amines, a factor that may also have occurred in the North Wales cohort.

### Developmental and Reproductive Effects

BZT has not been tested in developmental or reproductive studies. 2MBZT has been tested in a range of studies with mixed results. This may be because various different test protocols were used. A one-generation range-finding study in rats administered 2MBT in the diet found effects on body weight at all dose levels, with the lowest-observed-adverse-effect level (LOAEL) reported to be 357 mg/kg/d. However, the follow-up developmental study was conducted by gavage and found no body-weight effects and a NOAEL of 300 mg/kg/d for nonspecific clinical effects (urine staining, salivation) (Monsanto undated, as summarized in Whittaker et al. 2004). Rabbit developmental studies via gavage did not find fetotoxicity or teratogenicity in spite of evidence of maternal toxicity (decreased body weight at all doses down to 150 mg/kg/d; maternal lethality at 1000 mg/kg/d). A rat developmental study also did not find gross external malformations from gavage doses as high as 2200 mg/kg/d to dams during gestation, although this was only a range finding study without detailed examination of fetuses (Monsanto undated, as summarized in Whittaker et al. 2004). When rats were administered 200 mg/kg/d 2-MBZT via ip injection for d 1–15 of gestation, there was no evidence of maternal toxicity, fetal toxicity, or teratogenesis (Hardin et al. 1981).

In a 2-generation dietary study, rats were administered 4 different concentrations of 2-MBZT ranging from 179–1071 mg/kg. Exposure began 10 wk before mating and continued until 88 d postweaning. The LOAEL for decreased body weight gain was determined to be 179 mg/kg/d across the 2 generations, but there were no marked effects on fertility or other reproductive parameters (Springborn nd).

However, other studies suggest fetotoxic and teratogenic effects. Up to 20% of the chicken embryos injected with 0.1–2  $\mu\text{mol/egg}$  of 2MBZT were found to display malformations such as eye, neck, and back defects, as well as open coelom (Korhonen et al. 1983). A study in mice evaluated the response of several different strains to doses up to 464 mg/kg/d on d 6–15 of gestation. 2MBZT was associated with fetal malformations in two of the strains, with confirmatory results for one of the strains in a follow-up study (Bionetics Research Labs 1968). In a high-dose study in mice, subcutaneous injection of 4176 mg/kg/d of 2-MBZT on d 6–14 of gestation yielded fetotoxicity and a number of fetal malformations involving the ears, eyes, and gastrointestinal tract (Hanssen and Henderson 1991).

### Toxicity Values for Cancer and Noncancer Effects

There are no regulatory criteria or guidelines for BZT in drinking water or ambient air. The European Food Safety Authority set a limit for BZT in food of 0.5 ppm, but this is not associated with a specific toxicity value or acceptable daily intake (ADI). Toxicity values of three types are possible for BZT as follows:

1. Acute noncancer—The main concerns from short-term exposure are the potential for ocular and respiratory irritation and potential for sensitization. While there is no apparent information on whether BZT is a respiratory sensitizer, limited data on its respiratory irritant effects exist in mice. The  $\text{RD}_{50}$  studies from CPSC (2006) indicate that BZT is 18-fold less irritating in this mouse model system than formaldehyde, a reactive irritant gas that also induces hypersensitivity. The Connecticut Department of Public Health (CT DPH) has a residential indoor air guideline value for formaldehyde of 50 ppb ( $61.5 \mu\text{g}/\text{m}^3$ ), which is intended to prevent acute effects such as irritant and hypersensitivity reactions. This target level is supported by the Agency for Toxic Substances

and Disease Registry (ATSDR) minimum risk level (MRL) for formaldehyde (30 to 40 ppb subchronic to acute exposure) and by the target indoor air level for formaldehyde set by Health Canada (40 ppb) (ATSDR 1999; Health Canada 2006). Based upon the ratio of  $RD_{50}$ s between BZT and formaldehyde, a target BZT acute air guideline would be in the vicinity of  $1100 \mu\text{g}/\text{m}^3$ . However, the acute database for BZT is limited with no data in humans. This and the considerable uncertainty in the extrapolation across chemicals, especially with regard to relative sensitization potential, lead to a 10-fold database uncertainty factor and an acute air target of  $110 \mu\text{g}/\text{m}^3$ .

2. Chronic noncancer—A reference concentration (RfC) type value has been derived by New York State as part of its artificial turf exposure and risk assessment report (NYSDEC 2009). The New York State Department of Environmental Conservation (NYSDEC 2009) used the unpublished and European Food Safety Authority (EFSA)-reviewed 1971 study with BZT in which the only dose level (5.1 mg/kg/d) was without effect to derive an RfD of  $5 \mu\text{g}/\text{kg}/\text{d}$  based upon a cumulative 1000-fold uncertainty factor. This target is based upon the only BZT repeat dose study available and that study has limited reporting of data and only one dose level. However, it is consistent with the NOAEL for kidney effects in the 2-yr NTP bioassay of 2-MBT: 14 mg/kg/d. If a cumulative 1000-fold factor were applied to that NOAEL (10 for cross-species, 10 for intraspecies, 10 for data gaps and extrapolation across chemicals), the oral target would be  $14 \mu\text{g}/\text{kg}/\text{d}$ , similar to the  $5 \mu\text{g}/\text{kg}/\text{d}$  derived from the only BZT study. This value can be converted via dose-route extrapolation to an RfC of  $18 \mu\text{g}/\text{m}^3$ . The 2-MBZT developmental database does not suggest a greater noncancer potency, as the results were conflicting and where effects were seen it was at high dose.
3. Cancer unit risk—The CT DPH considers BZT as a possible carcinogen, given its positive mutagenicity and carcinogenic effects

of the related chemical 2MBZT in rodent and epidemiology studies. A 10-fold uncertainty factor for possible cancer effect could be applied to the BZT RfC described earlier, but that would make the cumulative uncertainty factor 10,000-fold, which is higher than the range commonly used by the U.S. Environmental Protection Agency (EPA) in establishing an RfC (up to 3000-fold). Use of a threefold carcinogen uncertainty factor leads to an RfC of  $6 \mu\text{g}/\text{m}^3$  or  $1.7\text{E-}03 \text{ mg}/\text{kg}/\text{d}$  on an oral dose route extrapolation basis. That target is coincidentally the 1 in a million cancer risk level based upon the 2MBZT cancer slope factor derived by Whittaker et al. (2004). That calculation is:

$$\begin{aligned} &1.7\text{E-}03 \text{ mg}/\text{kg}/\text{d} \\ &\times 6.34\text{E-}04/\text{mg-kg-d} \\ &= 1.08\text{E-}06 \text{ cancer risk} \end{aligned}$$

The current risk assessment utilizes the cancer slope factor for 2MBZT of  $6.34\text{E-}04/\text{mg-kg-d}$  based upon the male rat renal tumor response in the NTP bioassay described above. This was derived by Whittaker et al. (2004), who used linear modeling from a benchmark dose point of departure, as is standard practice for low-dose extrapolation for genotoxic carcinogens. Whittaker et al. (2004) relied upon this as the most sensitive endpoint but did not show cancer slope comparisons for the other tumor targets in the NTP study. DPH converted the oral slope factor to an inhalation unit risk by assuming  $20 \text{ m}^3$  air breathed per day for a 70-kg adult to yield  $1.8\text{E-}07/\mu\text{g-}\text{m}^3$ .

## DISCUSSION

Overall, the studies conducted on BZT and 2-MBZT indicated that BZT may pose a health risk at sufficiently high exposure. Exposure to BZT may result in central nervous system (CNS) depression, liver and kidney damage, dermatitis, and pulmonary irritation. BZT has the potential to be mutagenic and

carcinogenic. This latter conclusion is predicated to some degree on analogy with 2MBZT, an imperfect comparison due to differences in structure and metabolic pathways. The mechanistic concern with BZT is ring opening from oxidative metabolism with the formation of hydroxylamines, which are known risk factors for bladder cancer. 2MBZT undergoes side-chain conjugation, leaving the ring structure intact. In spite of these metabolic differences, the main cancer target of 2MBZT in human studies has been the bladder, with renal cancer and several other endpoints targets in rats. This suggests a link between the mechanism of action for these two thiazoles that would target the bladder, although more research is needed. BZT has been recommended with high priority for NTP carcinogenesis testing (NTP 1997) but has yet to receive such testing.

The wide degree of uncertainty in the toxicology database is somewhat mitigated by the fact that BZT exposure is common in foods and has a relatively high acceptable daily intake as set by FDA. However, studies of BZT exposure or health effects from food consumption have not been reported. The exposure route in the synthetic turf risk assessment is inhalation rather than oral. Although dose route extrapolation was performed from a BZT dietary study to the inhalation route, this is an uncertain extrapolation due to the possibility of first pass metabolic effects in the liver.

The screening level toxicity values derived presently for BZT for acute and chronic exposure are intended to be health protective. The RfD for BZT derived by NYSDEC (2009) makes reasonable use of the only repeat dose study and the RfD, so derived is consistent with a possible RfD derivation for 2MBZT. The lack of cancer bioassay data for BZT would normally preclude its entry into cancer risk assessment, creating the implicit assumption that it has zero potency. Our use of a published potency factor for 2MBZT enables this potential carcinogenicity to be factored into the BZT risk assessment. While there remains a large degree of uncertainty for the acute, chronic, mutagenic, and carcinogenic effects of BZT, the

current approaches are a reasonable starting point for including BZT in a crumb rubber risk assessment.

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