Company Notice of Filings for DIBASIC ESTERS

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[INSTRUCTIONS: Please utilize this outline in preparing tolerance petition submissions. In cases where the outline element does not apply please insert "NA-Remove" and maintain the outline. The comment notes that appear on the left margin represent hidden typesetting codes designed to expedite the processing of the FEDERAL REGISTER document. Please do not remove or alter these codes or change the margins in your submission. Simply type the information requested starting after the heading.

1. **[*Whitmire Micro-Gen Research Laboratories, Inc.*]**

PP **[*#5E4442*]**

EPA has received a pesticide petition (*PP* **[*#5E4442*]**)from **[*Whitmire Micro-Gen Research Laboratories, Inc.*]**, **[*3568 Tree Court Industrial Bvd., St. Louis MO 63122-6682*]**. proposing pursuant to section 408(d) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 346a(d), to amend 40 CFR Part 180 to establish an exemption from the requirement of a tolerance for **[*Dibasic esters (DBE)*]**. EPA has determined that the petition contains data or information regarding the elements set forth in section 408(d)(2) of the FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

DBE is a colorless liquid that consists of a mixture of dimethyl glutarate (55-75%), dimethyl adipate (10-25%), and dimethyl succinate (19-26%). The identity and properties of each component of DBE is summarized in the table below.

DBE Component	CAS #	Formula	MW	Density
Dimethyl succinate	106-65-0	$CH_3OOC(CH_2)_2COOCH_3$	146.14	1.12
Dimethyl glutarate	1119-40-0	$CH_3OOC(CH_2)_3COOCH_3$	160.17	1.09
Dimethyl adipate	627-93-0	$CH_3OOC(CH_2)_4COOCH_3$	174.20	1.06

1. *Plant metabolism*. **[*NA-REMOVE*]**.
2. *Analytical method.* **[**DBE vapors may be detected by gas chromatography using a flame ionization detector, for which a detection limit of 0.7 ug/L has been reported (Morris et al. 1991). In aqueous media, DBE may be detected by high pressure liquid chromatography using a diode ray detector, for which no detection limit was reported (Bogdanffy et al. 1991)**].**

3. *Magnitude of residues.* [NA-REMOVE].

B. Toxicological Profile

1. *Acute toxicity*. **[**Acute (24 hours) dermal contact with DBE produced mild to severe erythema and mild edema in rabbits exposed to undiluted DBE (Sarver, 1989). Fourteen-day dietary exposure to large concentrations of DBE in feed (10,000, 20,000, or 50,000 ppm) did not produce any gross or microscopic pathological changes in rats (Henry, 1981). Body weight gain was slightly reduced in a dose-dependent manner at the end of the exposure period. This study identified a NOEL of 10,000 ppm (842 mg/kg-day). Similarly, body weight gains were significantly reduced in rats exposed via inhalation to concentrations of 0.4 and 1.0 mg/L DBE for 6 hours/day, 5 days/week for 2 weeks (Alvarez, 1988). In both studies, however, decreases in body weight gain appear to be attributable to a dose-dependent decreases in feed consumption, rather than a pathological change caused by treatment**]**.

2. *Genotoxicity*. **[**DBE was not mutagenic in a *Salmonella typhimurium* assay in the presence or absence of a rat liver activation system (Koops, 1977; Arce, 1988). A significant increase in chromosomal aberrations was observed *in vitro* in human lymphocytes when metabolically activated (using a rat liver S-9 fraction), but not in the absence of metabolic activation (Vlachos, 1987). However, in an *in vivo* mouse bone marrow micronucleus assay, no significant increase in micronucleated cells were observed (Rickard, 1987)**]**.

3. *Reproductive and developmental toxicity*. **[**No effects on fetal survival, fetal weight, litter size, implantation, or the incidence of terata were observed in rats exposed via inhalation to concentrations 0.16, 0.4, or 1.0 mg/L DBE on days 7 through 16 of gestation (Alvarez, 1988). In addition, no treatment-related effects were observed for various reproduction indices (male fertility, female fertility, born alive, viability, gestation, and lactation) in rats exposed via inhalation to 0.16, 0.4, or 1.0 mg/l DBE for 14-weeks prior to mating, and continuing through breeding (15 days), gestation (21 days), and lactation (21 days). Pup weights were significantly reduced at concentrations of 1.0 mg/L DBE, however, this appears to be attributable to decreased food intake and body weight gain in maternal animals, which were significantly depressed at concentrations of 0.4 mg/L and higher (Kelly, 1988)**]**.

4. *Subchronic toxicity.* **[**In rats exposed via inhalation to 0.02, 0.08, or 0.40 mg/L DBE for 6 hours/day, 5 days/week, for 14 weeks, the only histopathological change of significance included mild squamous metaplasia in the olfactory epithelium (Kelly, 1987). Slight changes in liver weight, body weight, and blood calcium and sodium levels were also reported, however, these

were considered to be of minimal biologic significance. A no effect concentration was not identified for nasal effects. However, for systemic effects, the highest concentration tested (0.4 mg/L) was considered to be a NOEL**]**.

5. *Chronic toxicity*. **[**In rats exposed via inhalation to 0.16, 0.4, or 1.0 mg/L DBE for 22 weeks, the only histopathological change of significance included squamous metaplasia in the olfactory epithelium (Kelly, 1988). The incidence and severity of the nasal lesions was greater in this study in comparison to the 14-week study discussed above. A no effect concentration was not identified for nasal effects**].**

6. *Animal metabolism*. **[**The compounds that comprise DBE are derivatives of three naturally occurring dicarboxylic acids (adipic, glutaric and succinic acids). Specifically, DBE consists of dimethyl esters of these three acids. Due to the presence of carboxylesterases and other diesterases in mammalian tissues, these dimethyl esters are rapidly cleaved in the body to form their corresponding dicarboxylic acids: adipic, glutaric and succinic acids**].**

7. *Metabolite toxicology*. **[**By the oral route, the toxicity of DBE metabolites is low. The principle metabolites of DBE are naturally occurring dicarboxylic acids: succinic, glutaric, and adipic acids. Adipic and succinic acids are classified as Generally Recognized As Safe (GRAS) by the U.S. Food and Drug Administration for substances directly added to human food (CFR 184.1). Although glutaric acid is not classified as GRAS, its relative safety can be inferred since its carbon chain length (5) is intermediate of adipic (6) and succinic (4) acids. The dicarboxylic acids are substrates for glycolytic and gluconeogenic reactions in the cell, and as such, the components of DBE possess nutritional value (Ladriere et al. 1996).

By the inhalation route, the metabolites of DBE are irritants to the nasal mucosa, and are likely responsible for the metaplasia of the olfactory epithelia observed in exposed rats. *In vitro* studies indicate that inhibition of nasal carboxylase activity reduces the toxicity in rat nasal explants (Trela and Bogdanffy, 1991). In the rat, carboxylesterases appear to be preferentially localized in cells of the Bowman's gland and sustentacular epithelial cells which are immediately adjacent to olfactory nerve cells (Olson et al. 1993)**]**.

8. *Endocrine disruption*. **[**Mono- and dimethyl esters of succinic acid are capable of stimulating insulin release in rats (Vicent et al. 1994; Ladriere et al. 1996). However, rather than evidence of endocrine disruption, this observation is likely attributable to the nutritional value of DBE**]**.

C. Aggregate Exposure

1. *Dietary exposure*. **[**Dietary exposure due to use of DBE as an antifreeze agent is believed to be minimal, as is discussed for food and drinking water below**].**
2. *Food*. **[**DBE is not intended to be directly applied to foods. Rather, the use of DBE in pesticide formulations for food handling areas will be limited to sprays and aerosols for crack/crevice applications. Any incidental dietary exposure to DBE from such uses will be

minimal in comparison to the currently permitted use of DBE component, dimethyl succinate, as a food additive in beverages, ice cream, candy, and baked goods (CFR 21.3.170-199). Furthermore, the levels of dimethyl esters present in food as a result of DBE application in food areas are likely to be far less, on a molar equivalent basis, than the levels of naturally occurring dicarboxylic acids present in foods**].**

3. *Drinking water*. **[**Because DBE-containing pesticide formulations are not applied to agricultural crops, its migration to groundwater aquifers or to surface water bodies that may serve as suitable sources of drinking water is not anticipated.**].**

4. *Non-dietary exposure*. **[**The greatest potential for exposure to DBE is to pesticide applicators, who may be exposed via inhalation or dermal routes. USEPA's Pilot Interdisciplinary Risk Assessment Team (PIRAT, 1997) evaluated potential exposures to workers using a handwand applicator or a backpack applicator.

For the handwand applicator scenario, assuming a unit exposure of 29.178 mg/lb handled for the dermal pathway and a unit exposure of 1.063 mg/lb handled for the inhalation pathway, average daily doses of 0.03 and 0.001 mg/kg-day were calculated for dermal and inhalation exposures, respectively. In their calculations, USEPA conservatively assumed 100% absorption via both routes, a 70 kg body weight, an application rate of 0.08 lbs DBE/day for product containing 4.2% (w/w) DBE yielding a finish spray containing 0.065% DBE.

For the backpack applicator scenario, assuming a unit exposure of 482.581 mg/lb handled for the dermal pathway and a unit exposure of 0.329 mg/lb handled for the inhalation pathway, average daily doses of 1.0 and 0.007 mg/kg-day were calculated for dermal and inhalation exposures, respectively. In their calculations, USEPA conservatively assumed 100% absorption via both routes, a 70 kg body weight, an application rate of 0.14 lbs DBE/day for product containing 4.2% (w/w) DBE yielding a finish spray containing no more than 1% DBE**].**

D. Cumulative Effects

[Since exposures to DBE from food and drinking water are believed to be minimal, the potential for cumulative exposures (*i.e.*, summed across multiple routes of exposure) exceeding those estimated for pesticide applicators is very small. Furthermore, because the components of DBE are readily metabolized to polar, water-soluble metabolite, DBE is not expected to be persistent in biological tissues. Because DBE is irritating to the skin and nasal passages, any exposures are expected to be self-limiting. For these reasons, the potential for cumulative effects from exposure to DBE is low**].**

E. Safety Determination

1. *U.S. population*.**[**Potential dietary exposures to DBE are not likely to pose a significant risk to the general U.S. population. The components of DBE are dimethyl esters of three naturally occurring dicarboxylic acids (adipate, succinate, and glutarate), two of which are currently classified as GRAS by the U.S. Food and Drug Administration for direct addition to human

foods. It should be noted that the presence of methyl groups does not increase the toxicity of DBE. To the contrary, methylation is one of the metabolic pathways by which the body attempts to detoxify xenobiotics (Hodgson and Levi, 1987). As such, dimethyl succinate, dimethyl glutarate, and dimethyl adipate are likely to be less toxic than succinate, glutarate, and adipate, respectively. In support of this statement, Trela and Bogdanffy (1991) reported that succinate, glutarate, and adipate produced concentration-dependent increases in cytotoxicity in a rat nasal explant system. The cytotoxicity of DBE in the same system, however, was greatly diminished by a carboxylesterase inhibitor which effectively blocks the conversion of DBE to the dicarboxylic acids.

The potential hazards posed by DBE to pesticide applicators exposed via inhalation and dermal routes are low. For the handwand applicator, the average daily dermal and inhalation doses of 0.03 mg/kg-day and 0.001 mg/kg-day, respectively, are well below exposures which are believed to be without risk of deleterious effects (8.42 mg/kg-day for dermal exposures, and 0.38 mg/kg-day for inhalation exposures). Specifically, USEPA conservative assumptions for a worker applying a DBE-containing (4.2% w/w) product with a handwand maintain margin-of-exposures of 280 and 380 for dermal and inhalation exposures, respectively. Based on these margin-of-exposures, workers applying a hypothetical formulation containing 100% DBE would still be adequately protected. For the backpack applicator, the average dermal and inhalation doses of 1 and 0.007 mg/kg-day, are also below exposures which are believed to be without risk of deleterious effects. USEPA's conservative assumptions for a backpack applicator maintain a margin-of-exposure of 8 and 54 for dermal and inhalation exposures, respectively. Based on these margin-of-exposures, workers applying a hypothetical formulation containing 33% DBE would still be adequately protected. As this percentage far exceeds the levels anticipated for DBE-containing products, no concentration limit need be specified for DBE.**]**.

2. *Infants and children.* **[**There is no information available which suggests that infants and children are more highly exposed or are more susceptible to the effects of DBE. The lack of any significant toxicity in reproductive/developmental studies on DBE suggests the that growing organisms are not at increased risk. Since potential dietary exposures to infants and children are minimal based on anticipated use patterns, and since the toxicity of DBE by the oral route is very low, it is unlikely that these types exposures will result in any deleterious effects. Direct exposures to infants and children via the inhalation and dermal routes are not anticipated for the intended use of DBE**].**

F. International Tolerances

[Whitmire is not aware of any tolerances for DBE outside of the United States**].**