UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

February 28, 2007

SUBJECT: **Benzyl Benzoate: Risk assessment - Preliminary (Phase 1) HED Chapter of the Re-registration Eligibility Decision Document (RED). PC Code: 009501. Reregistration Case No. 4013. DP Barcode D327110.**

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Attached is Health Effect Division's preliminary risk assessment for Benzyl benzoate. Benzyl Benzoate is an insecticide/miticide registered for use to control dust mites in carpets, mattresses, upholstery, and on furniture, and to control mites on dogs. Benzyl benzoate is a member of the benzyl derivatives family, which is used in food flavors and fragrances, and occurs naturally in many foods. This document addresses exposures and risks from the commercial/residential uses. There are no registered agricultural or antimicrobial uses for benzyl benzoate.

The Team Reviewers who contributed to the disciplinary chapters are listed below:

Hazard Identification Assessment. HED memo of 10-12-06, Abdallah Khasawinah D322200.
HED's Revised Tox Chapter, memo of 01/31/07, Yan Donovan, D336083.
Occupational and Residential Exposure Assessment; James Miller, Environmental Scientist (D327111, 11/06/06)

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1.0 EXECUTIVE SUMMARY

A risk assessment is being conducted for the benzyl benzoate re-registration eligibility decision. Benzyl Benzoate is an insecticide/miticide used for control of dust mites in carpets, mattresses, upholstery, and on furniture, and for control of mites on dogs. Benzyl benzoate is a member of the benzyl derivatives family, which is used in food flavors and fragrances, and occurs naturally in many foods. Based on product labels, benzyl benzoate is formulated as a liquid spray (Aerosol) and as powder formulation; all are "ready-to-use" (RTU) products. Application rates vary depending upon the application method and use-site. There are no agricultural (food) uses for benzyl benzoate. The residential uses are limited to indoor treatments.

Benzyl benzoate has moderate acute toxicity by the oral route (LD_{50} = 2.8 g/kg, 2.24 g/kg, 1.68 g/kg in rats, cats, and rabbits, respectively) and low toxicity to dogs (LD_{50} = >22.44 g/kg). Clinical symptoms of acute oral toxicity in experimental animals are staggered gait, tremors, hypoactivity, lacrimation, hunched posture and prostration. Its acute inhalation toxicity is low to moderate (LC50 is > 5 mg/L in rats, Category IV)). It is slightly irritating to the rabbit eye and minimally irritating to the rabbit skin (Category IV). Benzyl benzoate induced developmental toxicity at very high doses in rats (850 mg/kg/day) but not at lower doses (625 mg/kg/day). A 1000 mg/kg/day dose did not cause any maternal toxicity. The developmental toxicity was expressed as decreased fetal body weight, ossification anomalies and increased fetal and litter incidence of wavy ribs. Benzyl benzoate was not tested in rabbits. Benzyl benzoate is hydrolyzed in vivo to yield benzyl alcohol and benzoic acid, an endogenous substance. Benzyl alcohol is oxidized to benzoic acid. Benzyl benzoate, like the other benzyl derivatives is readily absorbed from the gut, metabolized primarily in the liver, and excreted in the urine as glycine conjugates of benzoic acid (hippurate), or glucuronic acid conjugates (if glycine is depleted) or unconjugated metabolites. There is adequate information on benzyl benzoate metabolites: benzyl alcohol, benzoic acid and the benzoates and benzaldehyde.

Toxicology profiles of benzyl alcohol and benzaldehyde are also available. Endpoints were selected for benzyl benzoate based on benzyl benzoate and its metabolites benzyl alcohol and benzaldehyde. FQPA does not apply to benzyl benzoate since there are no food uses. No data base uncertainty factor is needed since no critical missing study was identified.

Benzyl benzoate was tested for mutagenicity and found negative in inducing unscheduled DNA synthesis in rat hepatocyte cultures, and it was not clastogenic nor did it cause mammalian cell gene mutations *in vitro*.

Benzyl benzoate was not tested for carcinogenicity, but its metabolite benzyl alcohol was tested in rats and mice. There was no evidence of carcinogenic activity of benzyl alcohol for male or female F344/N rats dosed with 200 or 400 mg/kg and for male or female $B6C3F_1$ mice dosed with 100 or 200 mg/kg for 2 years. Benzoic acid was tested as sodium benzoate in Swiss mice at 2% in water (4133 mg/kg/day for males and 3973 mg/kg/day for females) and caused no increased tumors. Based on the above information, benzyl benzoate is not expected to be carcinogenic.

The miticidal action of benzyl benzoate is not known. Based on its effects on vertebrates, it is presumed that it acts on the central nervous system of the mite resulting in death.

Benzyl benzoate is a non-food use pesticide based on the registered use pattern. Therefore, no dietary exposure is expected from insecticide/miticide uses of benzyl benzoate. No exposure from drinking water is expected either since all the registered uses are indoor uses. Benzyl benzoate is one of 37 benzyl derivatives (including benzyl esters) flavoring agents that were evaluated by the Joint Food and Agriculture Organization/World Health Organization, Joint Expert Committee on Food Additives (JECFA). Benzyl benzoate was evaluated by the JECFA at the 15th, 46th and 48th meetings and confirmed a group acceptable daily intakes (ADI) of 0-5 mg/kg bw. The estimated daily intake per person in Europe and the USA is 1900 µg and 4200 µg for benzyl benzoate, respectively. The JECFA committee concluded in its evaluation of the 37 benzyl derivatives used as flavoring agents including benzyl benzoate would not present safety concerns when used at current estimated levels.

Aggregate risk assessment includes residential exposures only. The short-term non-cancer residential handler risk assessment indicated that for all residential handler scenarios, risks do not exceed HED's level of concern (i.e., MOEs > 100). For residential post- application exposure, risks were assessed for both pre-vacuum and post-vacuum scenarios. Post-vacuum scenarios assumed 90% removal of the applied dose. The major routes of residential post application exposures are dermal for adults, dermal and incidental oral for Children. Inhalation exposure can be negligible due to the low vapor pressure of benzyl benzoate. Using the assumptions from HED's current residential SOPs, it is concluded that short-term residential post-application risks for all post-vacuum scenarios do not exceed HED's level of concern. Scenarios that exceeded HED's level of concern on the day of application (DAT = 0) are as follows:

For **pre-vacuum using the standard dermal loading model from the Residential SOPs:**

Adult

- Short-Term post-application general activities/shaker can: carpets, upholstery and furniture "Pre-Vacuum" (Dermal MOE = 12).

- Short-Term post-application general activities/aerosol spray: carpets, upholstery and furniture "Pre-Vacuum" (Dermal MOE = 50).

Child

- Short-Term post-application Combined (Dermal + Incidental oral)/ shaker can: carpets, upholstery and furniture "Pre-Vacuum" (MOE = 11).

- Short-Term post-application Combined (Dermal + Incidental oral)/ aerosol spray: carpets, upholstery and furniture "Pre-Vacuum" (MOE = 44).

Since the current screening model from the Residential SOPs for estimating dermal exposure is very conservative, a refined model (**equilibrium adherence model:** proposed by the risk assessment team and approved by HED's Exposure SAC) was also used in this assessment. This

model assumes that at equilibrium, the mass/area of exposed skin equals the mass/area of the treated area. Using the refinement model, the only scenario that exceeded HED's level of concern is:

For **pre-vacuum:**

- Child: Short-Term post-application Combined (Dermal + Incidental oral)/ shaker can: carpets, upholstery and furniture "Pre-Vacuum" (MOE = 80).

Risk Characterization

The Agency notes that the assessments were conducted for "**pre-vacuum**" and "**post vacuum"** scenarios. The purpose of the pre-vacuum assessment is that in a residential environment, entrance into a treated area is possible; therefore this assessment was conducted for this possibility. However, label specific directions indicated that vacuuming after an application is required and the Agency believes that the majority of the exposure would likely take place in a post-vacuumed environment; therefore, "**post-vacuum**" scenarios are more realistic. The assessed residential post-application risks are mainly from dermal risk. The toxicity profile of benzyl benzoate indicates that toxic effects only occur at high doses (90-day rat oral, 90-day mouse oral, and 16-day rat and mice oral), including developmental study, where only minor developmental effects (wavy ribs) occurred at 850 mg/kg/day. There is no systemic dermal toxicity at the limit dose of 1000 mg/kg/day in the 90-day rat dermal study. The above calculated dermal MOEs reflect HED's levels of concern for these minor toxicity effects.

Occupational Risk

The short- and intermediate-term occupational handler non-cancer risk assessment for benzyl benzoate indicated that risks do not exceed HED's level of concern (i.e., MOEs > 100). Product label information combined with exposure scenario activities, maintain that no occupational post-application scenarios exist.

Benzyl benzoate is not expected to be carcinogenic. No cancer risk assessment is needed.

2.0 INGREDIENT PROFILE

Benzyl benzoate is a member of the benzyl derivatives which are used in food flavors and fragrances, and occur naturally in many foods. Benzyl benzoate has a number of uses: As an antiparasitic insecticide that kills lice and the mites responsible for the skin condition scabies; As a fixative in fragrances to improve the stability and other characteristics of the main ingredients; As a food additive in artificial flavors; As a plasticizer in cellulose and other polymers; As a solvent for various chemical reactions.

2.1. Summary of Registered/Proposed Uses

Table 2.1 summarized the residential uses. Currently registered residential uses included: Tulsa (EPA Reg. No. 777-87), Benzyl Benzoate Technical (777-88), LeGear Mange Treatment (1910-

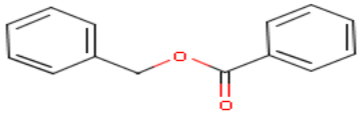
1), Sardex (2781-51), Raid Product 319 (4822-433), Raid product 420 (4822-480), Bissell Acarosan Dust Mite Powder (6297-6), Bissell Formula 555 (6297-7), Acarosan Moist Powder (59820-4), Benzyl Benzoate Technical Miticide (59820-5).

Table 2.1: Benzyl Benzoate Uses

Use Sites	Maximum Appl. Rate (Reg. #)	Maximum # Applications	Maximum amount of ai applied	Minimum Retreatment Interval (Days)	Application Methods
Residential Handler					
Carpets, Upholstery, Furniture, and Carpets	0.05 lb ai/Can (59820-4) (4822-433) (777-87) (6297-6) (6297-7) (4822-480)	As needed	0.05 (lb ai/Can)	NS	Shaker Can
			0.02 (lb ai/Can)		Aerosol (Spray
Pets (Dogs)	0.02 lb ai/Can (1910-1) (2781-51)	As needed	0.02 lb ai/Can	NS	Aerosol (Spray
Occupational Handler					
Pets (Dogs)	0.014 lb ai/Can (1910-1) (2781-51)	As needed	0.014 lb ai/Can	NS	Aerosol (Spray

2.2 Structure and Nomenclature

Product chemistry data were reviewed by RD. All pertinent product chemistry data requirements have been satisfied for the TGAI (RD memo of A. Smith, 10/20/98, D249552).

TABLE 2.2. Test Compound Nomenclature	
Chemical Structure	
Empirical Formula	$C_{14}H_{12}O_2$
Common name	Benzyl benzoate
Company experimental name	Not available
IUPAC name	Benzyl benzoate
CAS name	Benzoic acid, phenylmethyl ester
CAS Registry Number	120-51-4
End-use product/EP	Tulsa, Benzyl Benzoate Technical, LeGear Mange Treatment, Sardex, Raid Product 319, Raid product 420, Bissell Acarosan Dust Mite Powder, Bissell Formula 555, Acarosan Moist Powder, Benzyl Benzoate Technical Miticide
Chemical Class	insecticide/miticide
Known Impurities of Concern	None

2.3 Physical and Chemical Properties

TABLE 2.3. Physicochemical Properties		
Parameter	Value	Reference
Molecular Weight	212.2	MRID No.: 44552401
Boiling point/range	323°C at 760 mm Hg	MRID No.: 44552401, 44552501
pH	No measurable pH	MRID No.: 44552401, 44552501
Density	1.116 g/cm^3 @ 20°C	MRID No.: 44552401, 44552501
Water solubility (20 °C)	Insoluble	MRID No.: 44552401, 44552501
Solvent solubility (temperature not specified)	glycerol; ethanol; ether; acetone; benzene; methanol; chloroform; diethyl-phthalate	MRID No.: 44552401, 44552501
Vapor pressure (25°C)	4.5 mmHg @ 156°C, 760mm Hg @ 323 °C	MRID No.: 44552401, 44552501
Dissociation constant, pKa	None: Benzyl benzoate is a water insoluble aromatic organic ester.	MRID No.: 44552401, 44552501
Octanol/water partition coefficient, $Log(K_{OW})$ (25 °C)	3.60	MRID No.: 44552401, 44552501
UV/visible absorption spectrum	Peaks at 204, 230, 266, 282 nm in methanol.	MRID No.: 44552401, 44552501

3.0 METABOLISM ASSESSMENT

3.1 Rat Metabolic Profile

A rat metabolism study labeled with ^{14}C is not available. Benzyl benzoate is hydrolyzed in vivo to yield benzyl alcohol and benzoic acid, an endogenous substance. Benzyl alcohol is oxidized to benzoic acid. Benzyl benzoate, like the other benzyl derivatives is readily absorbed from the gut, metabolized primarily in the liver, and excreted in the urine as glycine conjugates of benzoic acid (hippurate), or glucuronic acid conjugates (if glycine is depleted) or unconjugated metabolites. (BENZYL DERIVATIVES (JECFA Food Additives Series 48) .

3.2 Nature of the Residue in Foods

No registered pesticide use on food items. Not applicable.

3.3 Environmental Degradation

No registered out door uses. Not applicable.

4.0 HAZARD CHARACTERIZATION/ASSESSMENT

4.1 Hazard Characterization

Benzyl Benzoate (See structure below) is an insecticide/miticide used for control of dust mites in carpets, mattresses, upholstery and on furniture, and for control of mites on dogs. It is a member of the benzyl derivatives which are used in food flavors and fragrances, and occur naturally in many foods.

"Benzyl benzoate is incorporated into lotions and ointments. It has been used for many years in veterinary and human medicine against mites and lice. When given in large doses to laboratory animals, benzyl benzoate causes excitement, incoordination, and paralysis of the limbs, convulsions, respiratory paralysis, and death. No human poisonings have been reported". (Recognition and Management of Pesticide Poisoning, 5th edition, 1999, http://npic.orst.edu/RMPP/rmpp_main2a.pdf)

Benzyl benzoate has moderate toxicity by the oral route (LD_{50} = 2.8 g/kg, 2.24 g/kg, 1.68 g/kg in rats, cats, and rabbits, respectively) and low toxicity to dogs (LD_{50} = >22.44 g/kg). (Graham *et al*, 1945 http://jpet.aspetjournals.org/cgi/content/citation/84/4/358). Clinical symptoms of acute oral toxicity in experimental animals are staggered gait, tremors, hypoactivity, lacrimation, hunched posture and prostration. Cats are also sensitive to the dermal toxicity of benzyl benzoate while in dogs and larger animals (horses, cows, sheep, and pigs) it is practically non toxic. Its acute inhalation toxicity is low to moderate (LC_{50} is > 5 mg/L in rats, Category IV)). It is slightly irritating to the rabbit eye and minimally irritating to the rabbit skin (Category IV)

Benzyl benzoate induced developmental toxicity at very high doses in rats (850 mg/kg/day) but not at lower doses (625 mg/kg/day). A 1000 mg/kg/day dose did not cause any maternal toxicity. The developmental toxicity was expressed as decreased fetal body weight, ossification anomalies and increased fetal and litter incidence of wavy ribs. Benzyl benzoate was not tested in rabbits.

Benzyl benzoate was tested for mutagenicity and found negative in inducing unscheduled DNA synthesis in rat hepatocyte cultures, and it was not clastogenic nor did it cause mammalian cell gene mutations *in vitro*.

Benzyl benzoate was not tested for carcinogenicity, but its metabolite benzyl alcohol was tested in rats and mice. There was no evidence of carcinogenic activity of benzyl alcohol for male or female F344/N rats dosed with 200 or 400 mg/kg and for male or female $B6C3F_1$ mice dosed with 100 or 200 mg/kg for 2 years (NTP 1989; http://ntp.niehs.nih.gov/index.cfm?objectid=07084CE8-A61F-27E1-3F68DFA12CEF826F). Benzoic acid was tested as sodium benzoate in Swiss mice at 2% in water (4133 mg/kg/day for males and 3973 mg/kg/day for females) and caused no increased tumors (http://www.epa.gov/iris/subst/0355.htm). IRIS considered benzoic acid as not classifiable as to human carcinogenicity based on absence of human data and inadequate data from animal bioassays. Based on the above information, benzyl benzoate is not expected to be carcinogenic.

Benzyl benzoate is readily absorbed through the skin. It has been reported that the *in vivo* dermal absorption of benzyl benzoate through the monkey skin was 70% of an applied dose within 24 hours.

In the following pages is a summary of the toxicology profiles of benzyl benzoate along with that of benzyl alcohol and benzaldehyde. Benzyl alcohol is a metabolite of benzyl benzoate which in turn is metabolized in experimental animals and humans to benzaldehyde and benzoic acid.

Table 4.1a. Acute Toxicity Profile – Benzyl Benzoate

Guideline No.	Study Type	MRID No.	Results	Toxicity Category
870.1100	Acute oral - rat	43896601	$LD_{50 =}$ 3,650 mg/kg in males $LD_{50 =}$ 2,804 mg/kg in females	III
870.1200	Acute dermal - rabbit	43896602	$LD_{50 >}$ 5000 mg/kg	IV
870.1300	Acute inhalation - rat	41881701, 41881801	$LC_{50 =}$ > 5.02 mg/L	III
870.2400	Eye irritation - rabbit	43896603	Slight irritant	III
870.2500	Dermal irritation - rabbit	43896604	Minimal irritant	IV
870.2600	Skin sensitization	43896605	Slight to moderate dermal sensitizer	

Table 4.1b Subchronic, Chronic and Other Toxicity Profile: Benzyl Benzoate

Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3250 90 - Day dermal toxicity - rats	43566901 (1994) **Acceptable/non-guideline**, 0, 40, 200 or 1000mg/kg/day. 6 hrs/day, 7 days/week for 13 weeks.	**Systemic LOAEL** = >1000 mg/kg/day **Systemic NOAEL** = 1000 mg/kg/day **Dermal LOAEL** = >1000 mg/kg/day **Dermal NOAEL =** 1000 mg/kg/day
870.3700a Developmental Toxicity- Rat: WIST HanIbm: WIST (SPF)	43025501 (1991) **Acceptable/guideline**, 25 time-mated females per group dosed via gavage at 0, 25, 125, 625, 850, or 1000 mg/kg/day from GD 6 through 15	**Maternal LOAEL** not established **Maternal NOAEL =** 1000 mg/kg/day (the highest dose tested. **Developmental Toxicity LOAEL** = 850 mg/kg/day based on decreased fetal body weight (90% of control) and ossification anomalies(in litters: 12/23 versus 2/24 in controls) and increased fetal and litter incidence s of wavy ribs (19/130 versus 2/148 in control and 10/23 versus 2/24 in control, respectively) **Developmental Toxicity NOAEL** = 625 mg/kg/day.
870.5550 Unscheduled DNA synthesis in primary rat hepatocytes	43413302 (1994) **Acceptable/guideline** Hepatocytes isolated from Wistar male rats were exposed for 18 hrs to 5 graded concentrations of test article, together with a constant amount (5uCi/mL) of tritiated thymidine.	Benzyl benzoate was negative for unscheduled DNA synthesis (UDS) in primary rat hepatocyte cultures exposed up to a precipitating concentration, 130 ug/mL.

Table 4.1b Subchronic, Chronic and Other Toxicity Profile: Benzyl Benzoate		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870-5375 *in vitro* mammalian chromosomal aberration assay – Human Lymphocytes	42023102(1991) **Acceptable/guideline** Lymphocytes were exposed for 4 hrs to solvent or graded concentrations of test material (+ or - S9)	Benzyl benzoate was moderately to severely toxic in non-activated cultures at 250 ug/mL, but not in activated cultures. Benzyl benzoate precipitated at concentrations above 500 ug/mL. Benzyl benzoate did not produce clastogenic effects and no increased chromosomal damage was evident at any concentration with or without S9 activation, nor in the incidence of polyploidy.
870-5300 (*in vitro* mammalian cell gene mutation assay - Chinese hamster lung fibroblast (V79 cells) – HGPRT locus: hypoxanthineguanine phosphoribosyl transferase	42023101 (1989) **Acceptable/guideline** V79 cell cultures exposed at of 10 to 120 ug/mL (-S9) at 50 to 500 ug/mL (+S9).	The test material precipitated at levels above 50 ug/mL +/- S9. Marked toxicity was observed at all nonactivated doses ≥ ug/mL in the first trial and at 150 ug/mL in the second trial. The S9-activated test material was not cytotoxic. It was concluded that benzyl benzoate was tested to the limit of solubility, and to cytotoxic levels (-S9) with no evidence of a mutagenic effect.

http://ntp.niehs.nih.gov/index.cfm?objectid=07084CE8-A61F-27E1-3F68DFA12CEF826F **Table 4.1c Subchronic, Chronic and Other Toxicity Profile: Benzyl Alcohol**		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
16-day study Rats and mice	None- Guideline (1989) – NTP Oral gavage 5/sex/dose 0, 125, 25, 500, 1000 or 2000 mg/kg/day	Doses above 1000 mg/kg/day were lethal. Blood around the mouth and nose, subcutaneous hemorrhages, and blood in the urinary and gastrointestinal tracts of rats and blood in the urinary bladder of mice. Animals were lethargic. NOAEL = 500 mg/kg/day
13-week study Rats	None- Guideline (1989) – NTP Oral gavage 10/sex/dose 0, 50, 100, 200, 400, and 800 mg/kg	LOAEL = 800 mg/kg/day based on reduced body weight gain and mortality at 800 mg/kg/day, neurotoxicity including staggering, respiratory difficulty, and lethargy. Hemorrhages occurred around the mouth and nose, and there were histologic lesions in the brain, thymus, skeletal muscle, and kidney. NOAEL = 400 mg/kg/day
13-week study Mice	None- Guideline (1989) – NTP Oral gavage 10/sex/dose 0, 50, 100, 200, 400, and 800 mg/kg	LOAEL = 800 mg/kg/day based on reduced body weight gain and mortality at 800 mg/kg/day, staggering. No compound-related histopathological findings. NOAEL = 400 mg/kg/day
2-year study Rats	None- Guideline (1989) – NTP Oral gavage 50/sex/dose 0, 200, or 400 mg/kg/day	Under the conditions of these 2-year gavage studies, there was no evidence of carcinogenic activity of benzyl alcohol for male or female F344/N rats dosed with 200 or 400 mg/kg. Survival in both dose groups of female rats was 50% that of vehicle controls, primarily due to an increased number of gavage-related deaths. There was no evidence of carcinogenic activity of benzyl alcohol for male or female $B6C3F_1$ mice dosed with 100 or 200 mg/kg for 2 years.
2-year study Mice	None- Guideline (1989) – NTP Oral gavage 50/sex/dose 0, 100, or 200 mg/kg/day	
Salmonella typhimurium strains TA98, TA100, TA1535, or TA1537.	None- Guideline (1989) – NTP	Benzyl alcohol was not mutagenic when tested by the preincubational protocol in the presence or absence of exogenous metabolic activation
mouse L5178Y/$TK^{+/-}$ lymphoma assay	None- Guideline (1989) – NTP	Benzyl alcohol induced an increase in trifluorothymidine (Tft)-resistant cells in the absence, but not in the presence, of S9; the effect was associated with toxicity.
cytogenetic assays with Chinese hamster ovary (CHO) cells	None- Guideline (1989) – NTP	Treatment with benzyl alcohol produced an increase in sister chromatid exchanges (SCEs) which was judged to be equivocal both with and without S9; a significant increase in chromosomal aberrations was observed after exposure to benzyl alcohol in the presence, but not the absence, of S9

http://ntp.niehs.nih.gov/index.cfm?objectid=070900A8-F3B0-B093-4CD9628A85D60F42 **Table 4.1d Subchronic, Chronic and Other Toxicity Profile: Benzaldehyde**		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
16-day study Rats and mice	None- Guideline (1990) – NTP Oral gavage 5/sex/dose 0, 800 or 1600 mg/kg/day – Rats 0, 1600 or 3200 mg/kg/day – mice	All rats that received 1,600 mg/kg died by day 2, and 2/5 males and 2/5 females that received 800 mg/kg died before the end of the studies. All mice that received 1,600 or 3,200 mg/kg died by day 3. Final mean body weights of dosed and vehicle control mice were similar. No gross lesions attributable to benzaldehyde were detected upon necropsy.
13-week study Rats	None- Guideline (1990) – NTP Oral gavage 10/sex/dose 0, 400, and 800 mg/kg/day	Six of 10 male rats and 3/10 female rats that received 800 mg/kg and 1/10 female rats that received 400 mg/kg died near the end of the studies. Final mean body weights of dosed and vehicle control rats were similar, with the exception of male rats receiving 800 mg/kg, which were 26% lighter than vehicle controls. Compound-related lesions seen in rats receiving 800 mg/kg, but not in those receiving 400 mg/kg, included degeneration and necrosis in the cerebellum, necrosis in the hippocampus, hyperplasia and/or hyperkeratosis in the fore stomach, and degeneration or necrosis of the liver and of the tubular epithelium in the kidney.
13-week study Mice	None- Guideline (1990) – NTP Oral gavage 10/sex/dose 0, 600, and 120 mg/kg/day	Nine of 10 male mice and 1/10 female mice that received 1,200 mg/kg benzaldehyde died by the end of the first week. Compound-related renal tubule degeneration and/or necrosis and reduction in final body weight were observed in the 600 mg/kg group of male mice. No reductions in body weight or compound-related lesions were seen in female mice.
2-year study Rats	None- Guideline (1990) – NTP Oral gavage 50/sex/dose 0, 200, or 400 mg/kg/day	Mean body weights of dosed rats and mice were similar to their respective vehicle controls throughout the studies. The survival of the high dose group of male rats was lower than that of the vehicle controls after 1 year; no other significant differences were observed between any groups of rats or mice (survival--male rats; vehicle control, 37/50; low dose, 29/50; high dose, 21/50; female rats: 33/50; 33/50; 29/50; male mice: 32/50; 33/50; 31/50, female mice: 30/50; 27/50; 35/50). Under the conditions of these 2-year gavage studies, there was no evidence of carcinogenic activity of benzaldehyde for male or female F344/N rats receiving 200 or 400 mg/kg per day. There was some evidence of carcinogenic activity of benzaldehyde for male or female B6C3F_1 mice, as indicated by increased
2-year study Mice	None- Guideline (1990) – NTP Oral gavage 50/sex/dose 0, 300, or 600 mg/kg/day	

http://ntp.niehs.nih.gov/index.cfm?objectid=070900A8-F3B0-B093-4CD9628A85D60F42 **Table 4.1d Subchronic, Chronic and Other Toxicity Profile: Benzaldehyde**		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
		incidences of squamous cell papillomas and hyperplasia of the fore stomach. Female rats and male and female mice might have been able to tolerate higher doses.
S. typhimurium	None- Guideline (1990) – NTP	Benzaldehyde was not mutagenic in six strains of S. typhimurium with or without exogenous metabolic activation.
chromosomal aberrations in CHO cells,	None- Guideline (1990) – NTP	Benzaldehyde did not induce chromosomal aberrations in CHO cells, with or without exogenous metabolic activation.
mouse L5178Y/TK$^{+/-}$ lymphoma assay	None- Guideline (1990) – NTP	Benzaldehyde induced increases in trifluorothymidine-resistant mouse lymphoma cells in the absence of exogenous metabolic activation.
cytogenetic assays with Chinese hamster ovary (CHO) cells	None- Guideline (1990) – NTP	Increased sister chromatid exchanges in CHO cells in both the presence and absence of metabolic activation.
Sex-linked recessive lethal mutations	None- Guideline (1990) – NTP	Sex-linked recessive lethal mutations were not induced in the germ cells of adult male D. melanogaster administered benzaldehyde by feeding or by injection.

4.2 Hazard Considerations for the Protection of Children

4.2.1 Adequacy of the Toxicity Data Base

The toxicology database for benzyl benzoate is limited to acute toxicity studies, a developmental study in rats, subchronic study (dermal) and mutagenicity tests. According to a memo dated November 27, 1990 from Nguyen Bich Thoa (HED) to P. Hutton (RD), these studies were required for the reregistration of the technical grade benzyl benzoate. However, there is adequate information on its metabolites: benzyl alcohol, benzoic acid and the benzoates and benzaldehyde purporting to the safe use of these chemicals in human foods.

4.2.2 Evidence of Neurotoxicity

Benzyl benzoate is neurotoxic at very high doses. When given in large doses to laboratory animals, benzyl benzoate causes excitement, incoordination, and paralysis of the limbs, convulsions, respiratory paralysis, and death.

4.2.3 Developmental Toxicity Studies

DEVELOPMENTAL – RAT

In a developmental toxicity study (MRID 43025501) benzyl benzoate (>99% purity) was administered in corn oil by gavage to 25 WIST HanIbm: WIST (SPF) mated female rats per dose group at dose levels of 0, 25, 125, or 625 mg/kg/day on gestational days (GDs) 6-15, inclusive. Because no maternal toxicity was observed at the highest dose level, three additional dose groups of 0, 850, and 1000 mg/kg/day were tested. Maternal toxicity was not observed in this study. Therefore, the maternal toxicity **NOAEL** is >1000 mg/kg/day (the limit dose and is the highest dose tested). The maternal toxicity **LOAEL** could not be determined. Developmental toxicity was observed at 850 and 1000 mg/kg/day in a dose related manner. It was manifested as significantly altered growth (decreased fetal body weight and delayed ossification) and increased fetal and litter incidence of wavy ribs. Also the percentage of post implantation loss increased significantly above control at 1000 mg/kg/day dose. The developmental toxicity **NOAEL** is 625 mg/kg/day and the developmental toxicity **LOAEL** is 850 mg/kg/day.

DEVELOPMENTAL – RABBIT

Developmental toxicity of benzyl benzoate was not evaluated in rabbits.

4.2.4 Reproductive Toxicity Study

Reproductive toxicity potential of benzyl benzoate was not evaluated.

There are no published studies available on benzyl benzoate teratogenicity or reproductive toxicity. However, benzyl benzoate is metabolized quantitatively to benzyl alcohol (which in turn is metabolized to benzaldehyde and benzoic acid) and benzoic acid. Therefore information

on these metabolites is useful in assessing these toxic parameters. The following is synopsis of a 2000 by WHO IPCS review of benzoic acid and sodium benzoate (http://www.inchem.org/documents/cicads/cicads/cicad26.htm). "For benzoic acid, two limited studies gave no indication of adverse reproductive or developmental effects. With sodium benzoate, several studies on different species have been performed, and embryotoxic and fetotoxic effects as well as malformations were seen only at doses that induced severe maternal toxicity. In a dietary study in rats, a NOAEL of about 1310 mg/kg body weight was established. Data on its precursors support the notion that benzoic acid is unlikely to have adverse reproductive effects at dose levels not toxic to the mother".

Other related materials; benzyl alcohol and benzyl acetate which metabolize to benzoic acid were not teratogenic either when tested at high doses. Thus "Benzyl acetate (0, 10, 100, 500, or 1000 mg/kg body weight per day by gavage on days 6-15) had no significant effects on maternal health in rats and did not induce changes in the numbers of corpora lutea, implantations, live or dead fetuses, or resorptions, implantation ratio, sex ratio, external or internal malformations, or placental weight. Fetal weights were significantly reduced at the highest dose (Ishiguro et al., 1993 as quoted from WHO IPCS Report)".

"Benzyl alcohol at 550 mg/kg body weight per day by gavage on days 6-15 of pregnancy had no effect on gestation index, average number of live pups per litter, postnatal survival, or pup body weight on days 0 and 3 in CD-1 mice (York et al., 1986), while 750 mg/kg body weight per day (days 7-14) induced a reduction in the pup weight and maternal weight gain, but no pup mortality or changes in mating or gestation indices, the total number of resorptions, or the number of live pups per litter (Hardin et al., 1987 as quoted from WHO IPCS Report)"

A WHO committee evaluated food additives and contaminants including benzyl derivatives and its findings are available in WHO Food Additives Series monograph 48 (http://www.inchem.org/documents/jecfa/jecmono/v48je14.htm). The following is an *ad verbatim* excerpt from this evaluation on the reproductive toxicity of benzyl derivatives: **"**At its forty-sixth meeting, the Committee reviewed a series of studies of developmental and reproductive toxicity with benzyl alcohol (No. 25), benzyl acetate (No. 23), benzyl aldehyde (No. 22), and sodium benzoate (Annex 1, reference *122*). The Committee concluded that: "Delayed development and reduced fetal and postnatal pup body weights were observed in developmental toxicity studies in rats, mice, hamsters and rabbits, but only at doses that were toxic to the mother. In a teratogenicity study with sodium benzoate, doses that induced severe maternal toxicity were associated with embryotoxic and fetotoxic effects and fetal malformations. A 4-generation study in rats showed no effect on growth, fertility, lactation or survival". The Committee concluded that the data reviewed were sufficient to demonstrate a lack of teratogenic and reproductive potential. No further studies on reproductive toxicity with benzyl derivatives in the group were available for review by the Committee at its present meeting".

4.2.5 Pre-and/or Postnatal Toxicity

4.2.5.1 Determination of Susceptibility

Benzyl benzoate induced developmental toxicity in rats at a high dose that did not produce maternal toxicity. The developmental toxicity was expressed as decreased fetal body weight, ossification anomalies and increased fetal and litter incidence of wavy ribs. Benzyl benzoate was not tested in rabbits. Tests on the related compounds: benzyl alcohol, benzoic acid and benzyl acetate did not demonstrate prenatal or postnatal toxicity.

4.2.5.2 Degree of Concern Analysis and Residual Uncertainties for Pre and/or Post-natal Susceptibility

Benzyl benzoate induced developmental toxicity at very high doses in rats (850 mg/kg/day) but not at lower doses (625 mg/kg/day). A 1000 mg/kg/day dose did not cause any maternal toxicity.

4.3 Safety Factor for Infants and Children.

4.3.1 Evidence that supports requiring a Developmental Neurotoxicity study

Benzyl benzoate is neurotoxic at very high doses that are also lethal. It also induces developmental toxicity at high doses that did not manifest maternal toxicity.

4.3.2 Evidence that supports not requiring a Developmental Neurotoxicity study

Since neurotoxicity occurs at very high doses that are lethal and developmental toxicity occurs at high doses that exceed any potential human exposure, the concern for any developmental neurotoxicity is low. HED concluded that no database uncertainty factor is needed.

4.4 Hazard Identification and Toxicity Endpoint Selection

4.4.1 Acute Reference Dose (aRfD) – General population, including infants and children.

This is not required, since there is no dietary exposure from the miticidal uses of benzyl benzoate.

4.4.2 Chronic Reference Dose (cRfD)

This is not required, since there is no dietary exposure from the miticidal uses of benzyl benzoate. The Joint FAO/WHO Joint Expert Committee on Food Additives (JECFA) evaluated benzyl benzoate at the 15^{th}, 46^{th} and 48^{th} meetings and confirmed a group ADI of 0-5 mg/kg bw for the benzyl derivatives.

4.4.3. Incidental Oral Exposure (short- term durations: 1 – 30 days)

Incidental oral exposure is likely from treated carpets and furniture and pet dogs treated with benzyl benzoate.

Study Selected: Developmental toxicity study in rats – Benzyl Benzoate

MRID: 43025501

Executive Summary: See Section 4.2.3

Dose and Endpoint: Maternal toxicity was not observed in this study. Therefore, the maternal toxicity **NOAEL** is >1000 mg/kg/day (the limit dose and is the highest dose tested).
Uncertainty Factor (UF): An Uncertainty Factor (UF) of 100 (10X for inter-species extrapolation, 10X for intra-species variability) was applied.

4.4.4. Incidental Oral Exposure (intermediate- term durations: 1 – 6 months)

Study Selected: 13-Week Study in rats – Benzyl Alcohol

Reference: National Toxicology Program (1989)

Executive Summary: Five- to six-week-old male and female F344/N rats (10/sex/group) were administered 0, 50, 100, 200, 400, or 800 mg/kg benzyl alcohol in corn oil by gavage, 5 days per week for 13 weeks. Eight of 10 male rats dosed with 800 mg/kg benzyl alcohol and 1 in the 200 mg/kg group died after being dosed; 1 vehicle control female rat, 1 in the 400 mg/kg group, and 2 in the 800 mg/kg group died after being dosed. Deaths in the vehicle, 200, 400 mg/kg/day groups and one death in the 800 mg/kg/day group were described as being accidental related to the gavage procedures. After dosing, rats of each sex in the 800 mg/kg group exhibited signs of neurotoxicity, including staggering, labored breathing, and lethargy. Blood around the nose and mouth was observed in 5/10 males after 8 weeks of chemical administration with 800 mg/kg benzyl alcohol. The final mean body weight of rats that received 800 mg/kg was 7% lower than that of the vehicle controls for males and 5% lower for females. Compound-related histopathologic effects observed at 800 mg/kg but not at lower doses included necrosis of the dentate gyrus of the hippocampus in 9/9 males and 7/7 females; skeletal muscle necrosis in 5/10 males; thymic congestion, hemorrhage, and atrophy in 8/10 males; and nephrosis in the kidney of 6/9 males. The renal lesions were not chemical specific and were similar to those seen in age related spontaneous renal disease, consisting of degeneration and regeneration of the tubular epithelium. Based on these findings, a LOAEL of 800 mg/kg/day is derived from this study and a NOAEL is 400 mg/kg/day.

Dose and Endpoint: a NOAEL of 400 mg/kg/day was derived based on reduced body weight gain and mortality at 800 mg/kg/day, neurotoxicity including staggering, respiratory difficulty, and lethargy. Hemorrhages occurred around the mouth and nose, and there were histologic lesions in the brain, thymus, skeletal muscle, and kidney.

Uncertainty Factor (UF): An Uncertainty Factor (UF) of 100 (10X for inter-species extrapolation, 10X for intra-species variability) was applied.

Comments about study/endpoint/UF: The NTP study selected is suitable for this exposure scenario. This NTP study evaluated the subchronic toxicity of benzyl alcohol, a metabolite of benzyl benzoate. In the absence of other studies with benzyl benzoate, this study with benzyl alcohol is appropriate for evaluating the subchronic toxicity of benzyl benzoate. Toxicity was observed following compound administration at 800 mg/kg/ dose in some of the animals. A companion NTP study in mice also produced similar toxic effects. This endpoint is conservative and is protective for infants and children, the most likely group to be exposed through this incidental oral route.

4.4.5 Dermal Exposure (short- term: 1-30 days)

Study Selected: Developmental toxicity study in rats – Benzyl Benzoate

MRID: 43025501

Executive Summary: See Section 4.2.3

Dose and Endpoint: For adults (including males and females), a NOAEL of 625 mg/kg/day was derived based on developmental toxicity at 850 mg/kg/day manifested as decreased fetal body weight, ossification anomalies and increased fetal and litter incidence of wavy ribs. This is conservative estimate for males since no maternal toxicity occurred at 1000 mg/kg/day. For children (all ages), a NOAEL of 1000 mg/kg/day was selected based on no maternal toxicity occurred at the limit dose.

Uncertainty Factor (UF): An Uncertainty Factor (UF) of 100 (10X for inter-species extrapolation, 10X for intra-species variability) was applied.

Comments about study/endpoint/UF: The point of departure is supported by a 90-day dermal study with benzyl benzoate in rats (MRID 43566901) where no systemic or dermal toxicity was observed at the highest dose (1000 mg/kg/day) tested. The oral toxicity endpoint is appropriate for this exposure scenario for adults because developmental toxicity was observed in the absence of maternal toxicity.

Dermal Absorption

No guideline study is available. Based on the results of literature search, in an *in vivo* dermal absorption study in monkeys, where 6 benzyl compounds (benzyl acetate, benzyl alcohol, benzyl benzoate, benzamide, benzoin and benzophenone) were evaluated, absorption through occluded skin was high for all compounds (approximately 70% of the applied dose in 24 hr) and no significant differences between the values for the different compounds were observed (Bronaugh RL, Wester RC, Bucks D, Maibach HI, Sarason R., Food Chem Toxicol. 1990 May;28(5):369-73). It was

concluded that humans may have significant systemic exposure to these fragrance materials. A 70% dermal absorption factor for benzyl benzoate is proposed based on this cited study.

4.4.6 Dermal Exposure (intermediate-term: 30-180 days)

Study Selected: 13-Week Study in rats – Benzyl Alcohol

Reference: National Toxicology Program (1989)

Executive Summary: see Section 4.4.4 above.

Dose and Endpoint: a NOAEL of 400 mg/kg/day was derived based on reduced body weight gain and mortality at 800 mg/kg/day, neurotoxicity including staggering, respiratory difficulty, and lethargy. Hemorrhages occurred around the mouth and nose, and there were histologic lesions in the brain, thymus, skeletal muscle, and kidney.

Uncertainty Factor (UF): An Uncertainty Factor (UF) of 100 (10X for inter-species extrapolation, 10X for intra-species variability) was applied.

Comments about study/endpoint/UF: The NTP study selected is suitable for this exposure scenario. This NTP study evaluated the subchronic toxicity of benzyl alcohol, a metabolite of benzyl benzoate. In the absence of other studies with benzyl benzoate, this study with benzyl alcohol is appropriate for evaluating the subchronic toxicity of benzyl benzoate. Toxicity was observed following compound administration at 800 mg/kg/ dose in some of the animals. A companion NTP study in mice also produced similar toxic effects.

There is a 90-day dermal study with benzyl benzoate in rats (MRID 43566901) where no systemic or dermal toxicity was observed at the highest dose (1000 mg/kg/day) tested. The 13-week study with benzyl alcohol is appropriate for this exposure scenario and is more conservative since the NOAEL is 400 mg/kg/day. A 70% dermal absorption factor is used.

4.4.7 Inhalation Exposure (short- Term: 1-30 days)

Study Selected: Developmental toxicity study in rats – Benzyl Benzoate

MRID: 43025501

Executive Summary: See Section 4.2.3

Dose and Endpoint: For adults (including males and females), a NOAEL of 625 mg/kg/day was derived based on developmental toxicity at 850 mg/kg/day manifested as decreased fetal body weight, ossification anomalies and increased fetal and litter incidence of wavy ribs. This is conservative estimate for males since no maternal toxicity occurred at 1000 mg/kg/day. For children (all age), a NOAEL of 1000 mg/kg/day was selected based on no maternal toxicity observed at the limit dose.

Uncertainty Factor (UF): An Uncertainty Factor (UF) of 100 (10X for inter-species extrapolation, 10X for intra-species variability) was applied.

Comments about study/endpoint/UF: There are no inhalation studies available for evaluating this exposure scenario. The oral toxicity endpoint is appropriate for this exposure scenario. A 100% absorption factor is assumed.

4.4.8 Inhalation Exposure (intermediate- term: 30-180 days)

Study Selected: 13-Week Study in rats – Benzyl Alcohol

Reference: National Toxicology Program (1989)

Executive Summary: See 4.4.4 above.

Dose and Endpoint: a NOAEL of 400 mg/kg/day was derived based on reduced body weight gain and mortality at 800 mg/kg/day, neurotoxicity including staggering, respiratory difficulty, and lethargy. Hemorrhages occurred around the mouth and nose, and there were histologic lesions in the brain, thymus, skeletal muscle, and kidney.

Uncertainty Factor (UF): An Uncertainty Factor (UF) of 100 (10X for inter-species extrapolation, 10X for intra-species variability) was applied.

Comments about study/endpoint/UF: See 4.4.6 above

Margins of Exposure

These are summarized in the following table:

Route	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	100	100	NA
Inhalation	100	100	NA
Residential (Non-Dietary) Exposure			
Oral	100	100	NA
Dermal	100	100	NA
Inhalation	100	100	NA

4.4.9 Recommendation for Aggregate Exposure Risk Assessments

When there are potential residential exposures to a pesticide, aggregate risk assessment considers exposures from three major routes: oral, dermal and inhalation exposures. For benzyl benzoate, incidental oral, dermal, and inhalation exposure for all durations can be aggregated since the toxicity effects are the same. A cancer aggregate risk assessment for benzyl benzoate is not required because there is no evidence of carcinogenicity.

4.4.10 Classification of Carcinogenic Potential

Benzyl benzoate was not tested for carcinogenicity, but its metabolite benzyl alcohol was tested in rats and mice. There was no evidence carcinogenic activity of benzyl alcohol for male or female F344/N rats dosed with 200 or 400 mg/kg and for male or female $B6C3F_1$ mice dosed with 100 or 200 mg/kg for 2 years (NTP 1989; http://ntp.niehs.nih.gov/index.cfm?objectid=07084CE8-A61F-27E1-3F68DFA12CEF826F). Benzoic acid was tested as sodium benzoate in Swiss mice at 2% in water (4133 mg/kg/day for males and 3973 mg/kg/day for females) and caused no increased tumors (http://www.epa.gov/iris/subst/0355.htm). IRIS considered benzoic acid as not classifiable as to human carcinogenicity based on absence of human data and inadequate data from animal bioassays. Based on the above information, benzyl benzoate is not expected to be carcinogenic.

Table 4.4. Summary of Toxicological Doses and Endpoints for benzyl benzoate for Use in Human Risk Assessments			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (Population	This is not required, since there is no dietary exposure from the miticidal uses of benzyl benzoate.		
Chronic Dietary (All populations)	This is not required, since there is no dietary exposure from the miticidal uses of benzyl benzoate. The Joint FAO/WHO Joint Expert Committee on Food Additives (JECFA) evaluated benzyl benzoate at the 15th, 46th and 48th meetings and confirmed a group ADI of 0-5 mg/kg bw for the benzyl derivatives.		
Incidental Oral Short- (1-30 days)	NOAEL= 1000 mg ai/kg/day	**Residential** MOE = 100 **Occupational** = 100	MRID: 43025501: based on developmental toxicity study where no maternal toxicity occurred at 1000 mg/kg/day.
Incidental Oral Intermediate-Term (1 - 6 months)	NOAEL= 400 mg ai/kg/day	**Residential** MOE = 100 **Occupational** = 100	NTP 1989: benzyl alcohol 13-week study in rats. Based on reduced body weight gain and mortality at 800 mg/kg/day, neurotoxicity: staggering, respiratory difficulty, and lethargy. Hemorrhages around the mouth and nose, and histologic lesions in the brain, thymus, skeletal muscle, and kidney.
Dermal: Short-(1 - 30 days)	**For adults including male and female:** Oral NOAEL= 625 mg ai/kg 70% dermal absorption **For children (all ages)**: Oral NOAEL= 1000 mg ai/kg/day. 70% dermal absorption	**Residential** MOE = 100 **Occupational** MOE = **100**	MRID: 43025501: based on developmental toxicity at 850 mg/kg/day manifested as decreased fetal body weight, ossification anomalies and increased fetal and litter incidence of wavy ribs. MRID: 43025501: based on developmental toxicity study where no maternal toxicity occurred at 1000 mg/kg/day.
Dermal: Intermediate- (1 - 6 months)	NOAEL=400 mg ai/kg/day 70% % dermal absorption	**Residential** MOE = 100 **Occupational** = 100	NTP 1989: benzyl alcohol 13-week study in rats. Based on reduced body weight gain and mortality at 800 mg/kg/day, neurotoxicity: staggering, respiratory difficulty, and lethargy. Hemorrhages around the mouth and nose, and histologic lesions in the brain, thymus, skeletal muscle, and kidney.

Table 4.4. Summary of Toxicological Doses and Endpoints for benzyl benzoate for Use in Human Risk Assessments			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Inhalation: Short – Term (1-30 days)	**For adults including male and female:** Oral NOAEL= 625 mg ai/kg. (Inhalation absorption rate = 100%)	**Residential** MOE = 100 **Occupational** MOE = **100**	MRID: 43025501: based on developmental toxicity at 850 mg/kg/day manifested as decreased fetal body weight, ossification anomalies and increased fetal and litter incidence of wavy ribs.
	For children (all ages): Oral NOAEL= 1000 mg ai/kg/day. (Inhalation absorption rate = 100%)		MRID: 43025501: based on developmental toxicity study where no maternal toxicity occurred at 1000 mg/kg/day.
Inhalation: Intermediate- (1 - 6 months)	NOAEL= 400 mg ai/kg/day (Inhalation absorption rate = 100%)	**Residential** MOE = 100 **Occupational** = 100	NTP 1989: benzyl alcohol 13-week study in rats. Based on reduced body weight gain and mortality at 800 mg/kg/day, neurotoxicity: staggering, respiratory difficulty, and lethargy. Hemorrhages around the mouth and nose, and histologic lesions in the brain, thymus, skeletal muscle, and kidney.
Cancer (Oral, dermal, inhalation)	Benzyl benzoate was not tested for carcinogenicity, but its metabolite benzyl alcohol was tested in rats and mice. There was no evidence carcinogenic activity of benzyl alcohol for male or female F344/N rats dosed with 200 or 400 mg/kg and for male or female B6C3F$_1$ mice dosed with 100 or 200 mg/kg for 2 years (NTP 1989; http://ntp.niehs.nih.gov/index.cfm?objectid=07084CE8-A61F-27E1-3F68DFA12CEF826F). Benzoic acid was tested as sodium benzoate in Swiss mice at 2% in water (4133 mg/kg/day for males and 3973 mg/kg/day for females) and caused no increased tumors (http://www.epa.gov/iris/subst/0355.htm). IRIS considered benzoic acid as not classifiable as to human carcinogenicity based on absence of human data and inadequate data from animal bioassays. Based on the above, benzyl benzoate is not expected to be carcinogenic.		

4.5 Endocrine disruption

EPA is developing a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of

potential effects in wildlife. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

4.6 FQPA Safety Factor

There are no pesticide uses on food items. Therefore, benzyl benzoate is not subject to the FQPA.

5.0 Public Health Data

5.1 Incident Reports

This will be addressed in a separate Agency memo.

6.0 EXPOSURE CHARACTERIZATION/ASSESSMENT

6.1 Dietary Exposure/Risk Pathway

No pesticide uses on food items. Therefore, no dietary exposure is expected from pesticide uses.

6.2 Water Exposure/Risk Pathway

No outdoor uses. No drinking water exposure from pesticide uses is expected.

6.3 Residential (Non-Occupational) Exposure/Risk Pathway

There is a potential for exposure in residential settings during the application process for homeowners who use products containing benzyl benzoate. There is also a potential for exposure from entering benzyl benzoate-treated areas that could lead to exposures to adults and children. Risk assessments have been completed for both residential handler (homeowner) and post-application scenarios.

Residential Handler Exposure Assessment

Residential handlers are addressed assuming homeowners complete all elements of an application without use of any protective equipment. Residential handler exposure scenarios are considered to be short-term. The quantitative exposure/risk assessment developed for residential handlers is based on applying powder via Shaker Can and applying a liquid via Aerosol Spray. The unit exposures were taken from the Pesticide Handlers Exposure Database (PHED) and a memorandum titled: MGK-264 Revised Occupational and Residential exposure assessment, dated 9/07/2005 (DP: D318873) and a Carbaryl study with (MRID 444598-01).

Short-term risks for residential handlers are presented below in Table 6.3a. For all exposure scenarios, risks are below HED's level of concern (i.e., MOEs are > 100) assuming handlers are wearing short-sleeve shirt, short pants, shoes, and socks. HED believes that the scenarios

assessed in this document represent worse-case exposures and risks resulting from use of benzyl benzoate in residential environments. It should also be noted that there were many other scenarios where medium to low quality PHED data were used to complete the assessment. Data quality should be considered in the interpretation of the uncertainties associated with each risk presented.

Table 6.3a: Summary of Residential Handler Exposure Estimates

Application. Equip.	***Exposure scenario***	***Max Appl. Rate***	***Daily Area Treated***	***Handler Scenario***	***Short-Term MOE***
		lbs ai/can	cans/day		Derml+Inhln Baseline
Shaker Can	Carpets, upholstery, and furniture	0.05	2	Powder	4,100
Aerosol Spray		0.02		Liquid	7,000
Aerosol Spray	Pets (Dogs)	.014	.5		39,000

Residential Post-application Exposures and Risks

Post-application exposure scenarios were developed for each residential setting where benzyl benzoate can be used. The major routes of residential post application exposures are dermal for adults, dermal and incidental oral for Children. Inhalation exposure can be negligible due to the low vapor pressure of benzyl benzoate. Assessments were conducted for "pre-vacuum" and "post vacuum" scenarios. The purpose of the pre-vacuum assessment is that in a residential environment, entrance into a treated area is possible; therefore this assessment was conducted for this possibility. However, label specific directions indicated that vacuuming after an application is required and the Agency believes that an 8 hour exposure time frame would take likely take place in a vacuumed environment, therefore MOEs reflecting post vacuum are more realistic scenarios.

Using the assumptions from HED's current residential SOPs, it is concluded that short-term residential post-application risks which exceeded HED's level of concern on the day of application (DAT = 0) are as follows:

For **pre-vacuum:**

- Adult: Short-Term post-application general activities/shaker can: carpets, upholstery and furniture "Pre-Vacuum" (Dermal MOE = 12).

- Adult: Short-Term post-application general activities/aerosol spray: carpets, upholstery and furniture "Pre-Vacuum" (Dermal MOE = 50).

- Child: Short-Term post-application Combined (Dermal + Incidental oral)/ shaker can: carpets, upholstery and furniture "Pre-Vacuum" (MOE = 11).

- Child: Short-Term post-application Combined (Dermal + Incidental oral)/ aerosol spray: carpets, upholstery and furniture "Pre-Vacuum" (MOE = 44).

Since the current SOPs is a standard screening model for estimating dermal exposure, which is very conservative, a refinement model (**equilibrium adherence model:** proposed by the risk assessment team and approved by HED's Exposure Sac) was used in this assessment. This model assumes that at equilibrium, the mass/area of exposed skin equals the mass/area of the treated area. For Benzyl Benzoate, the treated area refers to carpet and upholstery. Furthermore, a conservative estimate of 75% is assumed as hand transference with a remaining 25% transference rate for other body parts, a 100% transferal rate (Benzyl Benzoate powder to skin), and a toddler surface area of 0.7 sq. meters.

Using the refinement model, the only scenario that exceeded HED's level of concern for post application exposure is:

For **pre-vacuum:**

- Child: Short-Term post-application Combined (Dermal + Incidental oral)/ shaker can: carpets, upholstery and furniture "Pre-Vacuum" (MOE = 80).

A summary of risk estimates for residential post-application risks for adults and children is provided in the following tables. Additionally, HED combines risk values resulting from separate post-application exposure scenarios when toxicological effects are the same for all routes of exposure, and it is likely they can occur simultaneously based on the use-pattern and the behavior associated with the exposed population. In this case, dermal and incidental oral for children effects are the same, therefore combining these scenarios is necessary.

Table 6.3b: Adult Residential Risk Estimates for Post-application Exposure to Benzyl Benzoate

Exposure Scenario		TC cm^2/hr	Route Of Exposure	App. Rate (lbs ai/sq ft) Pre-Vacuum	App. Rate (lbs ai/sq ft) Post-Vacuum	S-Term Pre-vacuum MOE	S-Term Post-vacuum MOE
Indoors : Residential carpets, furniture and upholstery							
Gen. Activities	Shaker Can	16,700	Dermal	0.0008	0.00008	12	120
	Aerosol Spray			0.0004	0.00004	50	500
Indoors : Residential Pets (Dogs)							
Exposure Scenario		DAT Cans/day	Route of Exposure		Application Rate (lbs ai/can)	S-Term Adult MOE	S-Term Child MOE

Gen. Activities (petting, touching)	Aerosol Spray	0.5	Dermal	0.02	166,000	57,000

Table 6.3c: Child Residential Risk Estimates for Post-application Exposure to Benzyl Benzoate							
Exposure Scenario		TC cm^2/hr	Route of Exposure	App. Rate (lbs ai/sq ft) Pre-Vacuum	App. Rate (lbs ai/sq ft) Post-Vacuum	[1]S-Term Pre-vacuum MOE	[1]S-Term Post-vacuum MOE
Indoors : Residential carpets, furniture and upholstery (Linear Loading Model)							
Gen. Activities	Shaker Can	6000	Dermal	0.0008	0.00008	11	114
	Aerosol Spray			0.0004	0.00004	50	500
Indoors : Residential carpets, furniture and upholstery (Equilibrium Adherence Model)							
Gen .Activities	Shaker Can	6000	Dermal	0.0008	0.00008	120	1200
	Aerosol Spray			0.0004	0.00004	[2]N/A	[2]N/A
Indoors : Residential Incidental Oral (Linear Loading Model)							
Hand to Mouth	Shaker Can	N/A	Oral	0.0008	0.00008	240	2,400
	Aerosol Spray			0.0004	0.00004	960	9,600
Indoors : Combined Dermal and Incidental Oral Residential Incidental Oral (Linear Loading)							
Shaker Can	See Appendix B					11	110
Aerosol Spray						44	440
Indoors : Combined Dermal and Incidental Oral (Equilibrium Adherence Model)							
Shaker Can	See Appendix B					78	760
Aerosol Spray						[2]N/A	[2]N/A

Note:
[1]Level of Concern: MOE = 100
[2]N/A = Powder formulation is protective of Aerosol Spray.
Pre-Vacuum application rate = Post-app rate x 90% (vacuum removal %): Journal of Occupational and Environmental Hygiene; 3: 334-341, 2006

7.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. Since there are no pesticide food uses for benzyl benzoate, there fore, no food exposure from pesticide uses is expected. The registered residential uses are indoor uses and as a result, exposure from drinking water is not expected. Aggregate risk assessment included residential exposure only. See Section 6.3 above.

Risk Characterization

The assessed residential post-application risks are mainly from dermal exposures. The toxicity profile of benzyl benzoate indicated that toxic effects only occur at high doses (90-day rat oral, 90-day mouse oral, and 16-day rat and mice oral), including developmental study, where only minor developmental effects (wavy ribs) occurred at 850 mg/kg/day. There is no systemic dermal toxicity at the limit dose of 1000 mg/kg/day in the 90-day rat dermal study. The above calculated dermal MOEs (adults), combined dermal and incidental oral MOEs (Children) reflect HED's levels of concern for these minor toxicity effects.

Benzyl benzoate is one of 37 benzyl derivatives (including benzyl esters) flavoring agents that were evaluated by the Joint FAO/WHO Joint Expert Committee on Food Additives (JECFA). Benzyl benzoate was evaluated JECFA at the 15th, 46th and 48th meetings and confirmed a group ADI of 0-5 mg/kg bw. The estimated daily intake per person in Europe and the USA is 1900 µg and 4200 µg for benzyl benzoate, respectively. (BENZYL DERIVATIVES (JECFA Food Additives Series 48) . The JECFA committee concluded in its evaluation of the 37 benzyl derivatives used as flavoring agents including benzyl benzoate would not present safety concerns when used at estimated current levels.

7.1 Cancer Risk

Benzyl benzoate is not expected to be carcinogenic. No cancer risk assessment is required.

8.0 CUMULATIVE RISK CHARACTERIZATION/ASSESSMENT

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

EPA does not have, at this time, available data to determine whether benzyl benzoate has a common mechanism of toxicity with other substances. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to benzyl benzoate and any other substances and benzyl benzoate does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that benzyl benzoate has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 OCCUPATIONAL EXPOSURE/RISK PATHWAY

There is potential for exposure to benzyl benzoate in occupational scenarios from handling benzyl benzoate products during the application process and a potential for post-application worker exposure from entering into areas previously treated with benzyl benzoate. Based on the label use pattern, occupational post-application exposure scenarios are not expected.

9.1 Short/Intermediate-Term Handler Risk

HED uses the term "handlers" to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and that exposures can vary depending on the specifics of each task. Job requirements (e.g., amount of chemical to be used in an application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event. Short-, and intermediate-term dermal and inhalation exposures have been assessed for each occupational scenario. Long-term exposure is not expected.

The only formulation applied by the professionals is Shaker and Aerosol Spray Cans. No chemical specific information was available for benzyl benzoate handler exposure assessments, all analyses were completed using acceptable surrogate exposure data. The dermal and inhalation unit exposures were based on surrogate data from the Pesticide Handlers Exposure Database (PHED), MGK-264 Revised Occupational and Residential exposure assessment, dated 9/07/2005 (DP: D318873), and Carbaryl MRID 444598-01. It is assumed that the number of cans used per day is 10 cans, which is a professional estimate, whereas a data gap exists in this area. The application rate was calculated as described below.

Table 9.1: Summary of Short- and Intermediate-Term Benzyl Benzoate Occupational Handler Non-cancer Risks.

Exposure Scenario	Application Scenario	Appl. Rate (lb ai/can)	[1]DAT (cans/day)	[2]S-Term MOE (Dermal+Inhalation)	[2]I-Term MOE (Dermal+Inhalation)
				Baseline	Baseline
Applicator: Aerosol Spray					
Aerosol Spray	Pets (Dogs)	0.014	10	2,300	1,200

[1] Baseline PPE = (long sleeve shirt, long pants, no gloves, and no respirator)
[2] MOE = NOAEL/Daily Dose where the NOAEL for both dermal and inhalation is 625 mg/kg/day for Short-term and 400 mg/kg/day for Intermediate-term exposures.

9.2 Short/Intermediate-Term Post-application Risk

After reviewing label specific information on application rate and exposure scenario practices, the Agency believes that for the registered benzyl benzoate uses, no occupational post-application scenarios exist for Benzyl Benzoate. Listed below are the reasons for this decision.

- The products seeking re-registration are applied to prevent dust mites in carpets, mattresses, upholstery and on furniture, and for control of mites on dogs via shaker cans and aerosol spray. Concerning the registered uses on carpets, mattresses, upholstery and on furniture, the Agency believes that an occupational worker would use different equipment in-order to handle larger scale jobs, typically associated with occupational worker exposure scenarios that deal with a higher volume of application material. Therefore, an assessment for this type of application is not applicable. Secondly, the Agency believes that occupational settings involving pet care operators (dogs) are unique. Once the pet (dog) is treated, it leaves the treatment facility immediately; therefore there is little or no residue present after treatment. Therefore, a post-application exposure scenario is not applicable.

10.0 DATA NEEDS AND LABEL REQUIREMENTS

- Deposition of residue before and after vacuuming product.