UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

July 17, 2006

ACTION MEMORANDUM

SUBJECT: Reassessment of the One Exemption from the Requirement of a Tolerance for Maleic Anhydride (CAS # 108-31-6) and Maleic Acid (CAS # 110-16-7)

FROM: Pauline Wagner, Chief Pauline Wagner 7/17/06
Inert Ingredient Assessment Branch
Registration Division (7505P)

TO: Lois A. Rossi, Director
Registration Division (7505P)

I. FQPA REASSESSMENT ACTION

Action: Reassessment of one inert exemption from the requirement of a tolerance. The reassessment decision is to maintain the inert tolerance exemption "as-is."

Table 1. Tolerance Exemption Being Reassessed in this Document

CFR Citation				CAS Reg. No. CAS Name
40 CFR	**Inert Ingredients**	**Limits**	**Uses**	
180.920*	Maleic anhydride and maleic acid	For pesticide formulations applied to apples with a minimum preharvest interval of 21 days	Stabilizer	108-31-6 Maleic anhydride/ 2,5-Furandione 110-16-7 Maleic acid/ 2-Butenedioic acid (Z)-

*Residues listed in 40 CFR 180.920 are exempt from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops only.

Use Summary: Maleic anhydride and maleic acid are multi-functional chemical intermediates with many industrial applications. The primary use of maleic anhydride is in the manufacture of polyester and alkyd resins. These resins are added to fiberglass

reinforced plastics to make a strong and corrosion resistant material that is found in boats, auto, trucks, piping, and electrical goods. It is also used in the manufacture of lube oil additives, copolymers, dye intermediates, pharmaceuticals, textile chemicals, fumaric and malic acid, and other organic compounds. In addition, maleic anhydride is an ingredient in bonding agents used to manufacture plywood, a corrosion inhibitor, and a preservative in oils and fats.

List Reclassification Determination: The current List Classifications for maleic anhydride and maleic acid are 3. Because EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to maleic anhydride and maleic acid when used as inert ingredients in pesticide formulations, the List Classification for these chemicals will change from List 3 to List 4B.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the one inert ingredient exemption from the requirement of a tolerance for maleic anhydride (CAS # 108-31-6) and maleic acid (CAS # 110-16-7), and with the List reclassification determination, as described above. I consider the one exemption established in 40 CFR part 180.920 to be reassessed for purposes of FFDCA's section 408(q) as of the date of my signature, below. A Federal Register Notice regarding this tolerance exemption reassessment decision will be published in the near future.

Lois A. Rossi, Director
Registration Division

Date: July 24, 2006

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

July 24, 2006

MEMORANDUM

SUBJECT: Reassessment of the One Exemption from the Requirement of a Tolerance for Maleic Anhydride (CAS # 108-31-6) and Maleic Acid (CAS # 110-16-7)

FROM: Karen Angulo
Inert Ingredient Assessment Branch (IIAB)
Registration Division (7505C)

TO: Pauline Wagner, Chief
Inert Ingredient Assessment Branch (IIAB)
Registration Division (7505C)

Background

Attached is the science assessment for maleic anhydride and maleic acid. Maleic anhydride and maleic acid have one exemption from the requirement of a tolerance under 40 CFR 180.920 when used as inert ingredients (stabilizers) in pesticide formulations applied to growing crops only. This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, environmental fate, and ecotoxicity of maleic anhydride and maleic acid. The purpose of this document is to reassess the one existing exemption from the requirement of a tolerance for residues of maleic anhydride and maleic acid when used as inert ingredients (stabilizers) in pesticide formulations as required under the Food Quality Protection Act (FQPA).

Executive Summary

This report evaluates maleic anhydride and maleic acid, pesticide inert ingredients for which one exemption from the requirement of tolerance exists under 40 CFR 180.920 when they are used as stabilizers in pesticide formulations applied to apples, with a minimum pre-harvest interval of 21 days.

Maleic anhydride and maleic acid are multi-functional chemical intermediates with many industrial applications. The primary use of maleic anhydride is in the manufacture of polyester and alkyd resins. It is also used in the manufacture of lube oil additives, copolymers, dye

intermediates, pharmaceuticals, textile chemicals, fumaric and malic acid, and other organic compounds. Maleic acid is an intermediate in the production of maleic anhydride. While not as important economically as the anhydride, which is easier to use, maleic acid is used in the manufacture of alkyd and polyester resins, surface coatings, lubricant additives, plasticizers, copolymers, and textile chemicals. Both chemicals are approved for use as "indirect" food additives by the U.S. Food and Drug Administration (FDA).

Sufficient toxicity data and information are available to assess the hazards of maleic anhydride and maleic acid. This hazard assessment was developed using information from various sources, including the Organization for Economic Cooperation and Development (OECD) High Production Volume Chemicals Program, EPA's Integrated Risk Information System (IRIS), and the Hazard Substances Data Bank (HSDB). A qualitative assessment for all pathways of human exposure is appropriate given the minimal human health concerns associated with the low levels of exposure expected from the use of maleic anhydride and maleic acid as inert ingredients in pesticide formulations.

Available toxicological data indicate the relatively low acute toxicity of maleic anhydride and maleic acid by the oral and dermal routes of exposure. However, severe eye and skin irritation have been reported in animal studies for both chemicals. Maleic anhydride has also been shown to be a skin sensitizer and possible respiratory sensitizer. Maleic acid is not predicted to be either a skin or respiratory sensitizer. Subchronic and chronic toxicity studies indicate that respiratory tract and eye irritation are likely following repeated exposure to maleic anhydride and maleic acid. Effects on the kidneys have been observed in oral feeding studies at doses greater than or equal to 100 mg/kg/day. In addition, no neurotoxicity has been observed and no treatment-related reproductive or developmental effects are reported. Negative reproductive/developmental toxicity results for maleic acid can be inferred from the rapid hydrolysis of maleic anhydride to maleic acid. Maleic anhydride and maleic acid are also negative for genotoxicity.

Based on the rapid hydrolysis of maleic anhydride to maleic acid, the chemicals' ready biodegradability, and significant limits on their use as inert ingredients in pesticide products (apples only with a minimum pre-harvest interval of 21 days), the general population's exposure to maleic anhydride and maleic acid through diet (food and drinking water) and residential uses are not expected to occur at levels of concern. In addition, ecological risk concerns are not likely to occur. Maleic anhydride and maleic acid are not toxic to aquatic organisms. They are not persistent in the environment and bioconcentration in aquatic organisms is not expected to be significant.

Taking into consideration all available information on maleic anhydride and maleic acid, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to maleic anhydride or maleic acid when considering exposure through food commodities and all other non-occupational sources for which there is reliable information. Therefore, it is recommended that the one exemption from the requirement of a tolerance established for residues of maleic anhydride and maleic acid when used on growing crops under 40 CFR 180.920 can be considered reassessed as safe under section 408(q) of the Federal Food, Drug, and Cosmetic Act (FFDCA).

I. Introduction

This report provides a qualitative assessment for maleic anhydride and maleic acid, pesticide inert ingredients for which one exemption from the requirement of tolerance exists when used in pesticide formulations applied to growing crops only under 40 CFR 180.920. Maleic anhydride is readily hydrolyzed to maleic acid under aqueous conditions. Therefore, these two chemicals are presented together in this assessment.

II. Use Information

A. Pesticide Uses

Maleic anhydride and maleic acid are used as stabilizers in pesticide formulations applied to apples no less than 21 days before harvest. The one tolerance exemption for these chemicals is presented below in Table 1.

Table 1. Tolerance Exemption Being Reassessed in this Document

CFR Citation				CAS Reg. No. CAS Name
40 CFR	**Inert Ingredients**	**Limits**	**Uses**	
180.920*	Maleic anhydride and maleic acid	For pesticide formulations applied to apples with a minimum preharvest interval of 21 days	Stabilizer	108-31-6 Maleic anhydride/ 2,5-Furandione 110-16-7 Maleic acid/ 2-Butenedioic acid (2Z)-

*Residues listed in 40 CFR 180.920 are exempt from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops only.

B. Other Uses

Maleic anhydride and maleic acid are multi-functional chemical intermediates with many industrial applications. The primary use of maleic anhydride is in the manufacture of polyester and alkyd resins (U.S. EPA, 2006a). These resins are added to fiberglass reinforced plastics to make a strong and corrosion resistant material that is found in boats, auto, trucks, piping, and electrical goods. It is also used in the manufacture of lube oil additives, copolymers, dye intermediates, pharmaceuticals, textile chemicals, fumaric and malic acid, and other organic compounds. In addition, maleic anhydride is a preservative in oils and fats, a corrosion inhibitor, and. an ingredient in bonding agents used to manufacture plywood (HSDB, 2006).

Maleic acid is an intermediate in the production of maleic anhydride (OECD SIAP, 2004). It is recovered in the manufacturing process to be used as a raw material in the synthesis of tetrohydrofuran, fumaric acid, and 1,4-butanediol. While not as important economically as the anhydride, which is easier to use, maleic acid is used in the manufacture of alkyd and polyester resins, surface coatings, lubricant additives, plasticizers, copolymers, and textile chemicals (HSDB, 2006). It is also used in preparing the maleate salts of antihistamines and similar drugs, as well as a preservative for oils and fats.

Maleic anhydride and maleic acid are both approved for use as "indirect" food additives by the Food and Drug Administration (FDA). Both chemicals are used in food contact articles as adhesives and components of coatings, paper and paperboard components, and polymers. Maleic anhydride may also come into contact with food as an adjuvant and production aid. The indirect food additive uses are summarized below in Table 2.

Table 2. Uses of Maleic Acid and Maleic Anhydride as Specified in 21 CFR

21 CFR Citation	Use Pattern*
	Maleic Acid
175.105	As an indirect food additive, an adhesive used as a component of articles used in packaging, transporting, or holding food.
175.300	Resinous and polymeric coatings for food contact surfaces intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.
175.320	*Maleic acid*-modified copolymers in resinous and polymeric coatings used as the food-contact surface of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.
176.170	Vinyl chloride or vinyl acetate copolymers produced by copolymerizing vinyl chloride or vinyl acetate with *maleic acid* and used as components of the uncoated or coated food-contact surface of paper and paperboard intended for use in producing, manufacturing, packaging, processing, preparing, treating, packing, transporting, or holding aqueous and fatty foods.
177.1200	Basic Components of Single and Repeated Use Food Contact Surfaces. Limit for maleic acid is one percent.
177.2420	Cross-linked polyester resins produced by the condensation of *maleic acid* (or other listed chemicals) and used in articles or components of articles intended for repeated use in contact with food.

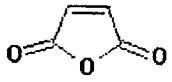
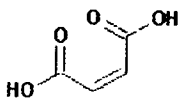
21 CFR Citation	Use Pattern*
	Maleic Anhydride
175.105	As an indirect food additive, an adhesive used as a component of articles used in packaging, transporting, or holding food.
175.300	Resinous and polymeric coatings for food contact surfaces intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.
176.170	Numerous processes involving the use of *maleic anhydride* to produce a chemical to be used as a component of the uncoated or coated food-contact surface of paper and paperboard intended for use in producing, manufacturing, packaging, processing, preparing, treating, packing, transporting, or holding aqueous and fatty foods.
176.180	Homopolymers and copolymers of *maleic anhydride* and its methyl or butyl esters when used as components of paper and paperboard intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding (in contact with) dry food.
177.1390	Adhesives formulated from *maleic anhydride* adduct of polypropylene used in food-contact articles produced from high-temperature laminates used to package all food types except those containing more than 8 percent ethyl alcohol.
177.1520	Ethylene-maleic anhydride copolymers containing no more than 2 percent by weight of copolymer units derived from *maleic anhydride* when used as a component of articles intended for use in contact with food.
177.1630	*Styrene-maleic anhydride resin*, partial 2-butoxyethyl ester, ammonium salt for use only as a coating for polyethylene phthalate films at levels not to exceed 0.025 gram per square meter of the film, in contact with certain food types used as, or components of plastics (films, articles, or fabric) intended for use in contact with food
177.1680	Polyurethane resins produced when one or more of the listed isocyanates is made to react with *maleic anhydride* and used as the food-contact surface of articles intended for use in contact with bulk quantities of dry food of a certain type.
177.1820	Styrene-maleic anhydride copolymers (produced by the polymerization of styrene and *maleic anhydride*) used as articles or components of articles intended for use in contact with food.
178.3870	Rosins and rosin derivatives (including salts of rosin manufactured by the partial or complete saponification of certain rosins or modified rosins with *maleic anhydride*) used in the manufacture of articles or components of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.

* The use patterns included in this table are summaries of those found in 21 CFR. Additional provisions and conditions apply. Other chemicals included in the approved uses have been omitted from the use pattern descriptions for clarity. See specific sections of 21 CFR for additional details.

III. Physical and Chemical Properties

Physical and chemical characteristics of maleic anhydride and maleic acid, along with their structure and nomenclature, are found in Table 3.

Table 3. Physical and Chemical Properties of Maleic Anhydride and Maleic Acid

Parameter	Maleic Anhydride	Maleic Acid	Reference
Structure			ChemFinder, 2006
CAS Number	108-31-6	110-16-7	HSDB, 2006
Molecular Formula	C4-H2-O3	C4-H4-O4	
Molecular Weight	98.06 g/mol	116.07 g/mol	
Odor	Irritating, choking	Faint acidulous	
Physical State	Colorless needles, white lumps or pellets	Colorless or white crystals	
Melting Point	52.8°C	138-139°C	
Boiling Point	202°C @ 760 mm Hg	135°C	
Water Solubility	Soluble, forming maleic acid (491 mg/L @ 25°C)*	Extremely soluble (788 g/L @ 25°C)	
Other Solubility	Soluble in ether, acetate, and chloroform.	Soluble in alcohol, acetone, and glacial acetic acid	
Vapor Pressure	2.5×10^{-1} mm Hg @ 25°C	3.59×10^{-5} mm Hg @ 25°C*	
Log K_{ow}	1.62*	-0.48	
K_{oc}	1*	NA	
Henry's Law Constant	3.93×10^{-6} atm-m^3/mol @ 25°C*	7×10^{-14} atm-m^3/mol	
Specific Gravity	1.48 @ 20°C	1.59 @ 20°C	

* Extrapolated/Estimated
NA – Not available

IV. Hazard Assessment

A. Hazard Profile

This hazard assessment was developed using the Screening Information Data Set (SIDS) on maleic anhydride and maleic acid, which was prepared by EPA and submitted to OECD under the SIDS High Production Volume Chemicals Program. Based on the data submitted, the SIDS Initial Assessment Profile (SIAP) for this submission concludes that maleic anhydride and maleic acid are "currently of low priority for further work" (OECD SIAP, 2004). Other sources of information used in this assessment include the U.S. EPA's Integrated Risk Information System (IRIS) (U.S. EPA, 2006b), the

Hazardous Substances Data Bank (HSDB, 2006), and Patty's Toxicology (Bingham et al., 2001).

B. Toxicological Data

Acute Toxicity:

Available acute toxicological information indicates the relatively low toxicity of maleic anhydride and maleic acid by the oral and dermal routes of exposure. Both chemicals are reported to be severely irritating to the skin and eyes of rabbits. In addition, maleic anhydride has been shown to be a skin sensitizer to guinea pigs, as well as a possible respiratory sensitizer to rats. Sensitization data are not available for maleic acid; however, it is not predicted to be either a skin or respiratory sensitizer. Quantitative data from published acute toxicity studies are summarized in the following table:

Table 4. Summary of Acute Toxicity Data for Maleic Anhydride and Maleic Acid

Study Type (Species)	Toxicity Value	Reference
Oral LD_{50} (rat, mouse, rabbit, guinea pig)	Rat: LD_{50} = 400 to 1050 mg/kg Mouse: LD_{50} = 465 mg/kg Rabbit: LD_{50} = 875 mg/kg Guinea Pig: LD_{50} = 390 mg/kg	OECD SIAP, 2004; HSDB, 2006
Dermal LD_{50} (rabbit)	LD_{50} = 1600 to 2600 mg/kg	OECD SIAP, 2004
Dermal/Eye Irritation (rabbit)	Severe skin and eye irritant	OECD SIAP, 2004
Dermal Sensitization (guinea pig)	Maleic Anhydride: skin sensitizer Maleic Acid: not predicted to be skin sensitizer	OECD SIAP, 2004
Respiratory Sensitization (rat)	Maleic Anhydride: possible respiratory sensitizer Maleic Acid: not predicted to be respiratory sensitizer	OECD SIAP, 2004

Repeated Dose Toxicity:

Subchronic and chronic toxicity studies indicate that respiratory tract and eye irritation are likely following repeated inhalation exposure to maleic anhydride and maleic acid. Effects on the kidneys have also been observed in oral feeding studies at relatively high doses.

In a repeat dose inhalation study, rats were exposed to maleic anhydride at concentrations of 0, 12, 32, or 84 mg/m^3 (0, 3, 8, or 21 ppm) for 6 hr/day for 4 weeks (OECD SIAP, 2004). Nasal, trachea, and lung irritation were evident at all exposure levels. Effects were concentration-related and included epithelial hyperplasia and the presence of inflammatory exudates in the nasal turbinates and trachea, and epithelia hyperplasia, squamous metaplasia, and intra-alveolar hemorrhage in the lung. Increased incidence of hemorrhagic lung foci were also observed in rats exposed to 32 and 86 mg/m^3. The lowest-observable-adverse-effect level (LOAEL) was 12 mg/m^3 (3 ppm).

Respiratory tract and eye irritation were observed in rats, hamsters, and monkeys following repeated inhalation exposures (6 hr/day, 5 days a week for 6 months) to maleic anhydride at concentrations of 0, 1.1, 3.3 or 9.8 mg/m^3 (0, 0.3, 0.8, or 2.4 ppm) (OECD SIAP, 2004; HSDB, 2006). Respiratory tract and eye irritation were observed in rats and hamsters exposed to 3.3 and 9.8 mg/m^3, and in monkeys exposed to 9.8 mg/m^3. Reductions in body weight were observed only in male rats exposed to 9.8 mg/m^3. In addition, hyperplastic and metaplastic changes of the nasal tissues were observed in both rats and hamsters. However, these changes are considered a sign of irritation and were reversible. The no-observable-adverse-effect level (NOAEL) for rats was 3.3 mg/m^3 (0.8 ppm), the highest dose tested.

Effects on the kidneys were observed in rats following the oral (diet) administration of maleic anhydride for 90 days (OECD SIAP, 2004). Effects occurred at relatively high doses (greater than or equal to 100 mg/kg/day) and were more severe in males than females. The effects occurred mainly in the tubular cells, with some effects occurring in the glomeruli. The kidney effects were likely due to maleic acid (known to cause kidney damage), since maleic anhydride rapidly hydrolyzes to maleic acid under aqueous conditions. However, no kidney effects were observed in male and female rats fed 0, 10, 32, or 100 mg/kg/day for 2 years (OECD SIAP, 2004; U.S. EPA, 2006b). In this study, slight to marginal decreases in body weight were observed at 32 and 100 mg/kg/day. The NOAEL for this study was 10 mg/kg/day. In addition, no adverse kidney effects were observed in a dietary study in dogs fed 0, 20, 40 or 60 mg/kg/day of maleic anhydride, 7 days a week for 90 days (OECD SIAP, 2004; U.S. EPA, 2006b). The LOAEL for this study was 60 mg/kg/day for hematological effects and the NOAEL was 40 mg/kg/day (U.S. EPA, 2006b).

In a multigeneration reproduction study, male and female rats administered maleic anhydride by gavage at 0, 20, 55 or 150 mg/kg/day experienced compound-related mortality and renal pathological changes at 150 mg/kg/day (U.S. EPA, 2006b). Multiple renal lesions occurred in surviving rats at all dose levels. The LOAEL for this study was 20 mg/kg/day. (This study is discussed in more detail under Reproductive/Developmental Toxicity.)

An oral Reference Dose (RfD) of 0.1 mg/kg/day was determined for maleic anhydride in 1993 by the U.S. EPA under the IRIS program (U.S. EPA, 2006b). The 2 year oral chronic study in rats and the oral multigeneration reproduction study in rats were the principal studies used in determining the RfD. A literature search conducted in 2002 identified one or more significant new studies which have not been included in IRIS at this time. In addition, IRIS states that "[i]t appears from the studies ... maleic anhydride is more toxic when administered by gavage than feed. Observed differences in toxicity may therefore be attributable to the route of administration."

Neurotoxicity:

A 1-hour inhalation exposure of rats to 0.72 mg/L of maleic acid produced generalized inactivity, hyperpnea and sedation within 15 minutes of exposure (HSDB, 2006). Gross necropsy revealed no significant findings. However, no neurotoxic effects have been reported in the available studies.

Genotoxicity:

Results of limited *in vitro* and *in vivo* genotoxicity tests conducted with maleic anhydride and maleic acid have been negative. On the basis of all the data on genotoxicity, a mutagenic effect is not assumed.

Maleic anhydride and maleic acid have both tested negative in bacterial gene mutation tests, with and without metabolic activation at doses up to 600 umol/plate (OECD SIAP, 2004; HSDB, 2006). In addition, maleic anhydride was negative in an *in vivo*, mammalian (rat) bone marrow chromosomal aberration test (OECD SIAP, 2004). An *in vitro* chromosomal test was positive for maleic anhydride both with and without metabolic activation (OECD SIAP, 2004). However, it was unclear if the positive results were due to maleic anhydride or to the acidic environment resulting from the hydrolysis of maleic anhydride to maleic acid.

Reproductive/Developmental Toxicity:

No treatment-related reproductive or developmental effects were reported in published animal studies following oral exposure to maleic anhydride. Negative results for reproductive and developmental toxicity of maleic acid can be inferred from the rapid hydrolysis of maleic anhydride to maleic acid.

In a multi-generation reproductive study, rats (10 males and 20 females per group) received 0, 20, 55 or 150 mg/kg/day of maleic anhydride via gavage and were mated to produce two generations, each with two litters (OECD SIAP, 2004; HSDB, 2006). Each generation was dosed for at least 80 days before mating. No adverse effects on fertility were noted with maleic anhydride at doses up to 55 mg/kg/day administered over two generations. However, maleic anhydride was toxic (mortality, body weight changes, and respiratory irritation) to the parental animals at 150 mg/kg/day. Histopathological effects were also observed in the kidney and bladder of the first generation parental animals. No adverse effects on litter size and on pup survival were noted at doses up to 150 mg/kg/day. The LOAEL for parental effects was 20 mg/kg/day The NOAEL for reproductive effects was 55 mg/kg/day (highest dose tested due to parental death at 150 mg/kg/day).

The potential teratogenic effects of maleic anhydride were investigated in adult rats approximately 12 weeks of age (OECD SIAP, 2004; HSDB, 2006). Female rats were treated via gavage with 0, 30, 90, or 140 mg/kg/day of maleic anhydride from day 6 to day 15 of gestation. Examination of the fetuses for external abnormalities, soft tissue abnormalities and skeletal abnormalities did not reveal any treatment-related effects. No

increases in fetal malformations were noted and the variations detected were similar in the control and treated groups. The maternal NOAEL was determined to be 140 mg/kg/day.

C. Metabolism and Pharmacokinetics

Somewhat limited information was available to assess the metabolism and pharmacokinetics of maleic anhydride and maleic acid (specifically, elimination from the body). Maleic anhydride is readily hydrolyzed to maleic acid under aqueous conditions. Unlike maleic acid, maleic anhydride has the potential to form haptens by acrylating with amino acids, resulting in an immunological response (dermal and respiratory sensitization) (OECD SIAP, 2004).

D. Special Considerations for Infants and Children

Maleic acid and maleic anhydride exhibit a relatively low order of toxicity for human health effects. No adverse effects on litter size and on pup survival were noted at doses up to 150 mg/kg/day. The LOAEL for parental effects was 20 mg/kg/day. The NOAEL for reproductive effects was 55 mg/kg/day (highest dose tested due to parental death at 150 mg/kg/day). Based on this information there is no concern, at this time, for increased sensitivity to infants and children to maleic acid and maleic anhydride when used as an inert ingredient in pesticide formulations. For the same reason, a safety factor analysis has not been used to assess risk and, therefore, the additional tenfold safety factor for the protection of infants and children is also unnecessary.

V. Environmental Fate Characterization and Drinking Water Considerations

The following is taken directly from EPA's report submitted to OECD under the SIDS High Production Volume Chemicals Program (OECD SIAP, 2004). Based on this information, contributions to drinking water are not expected from the inert ingredient use of maleic anhydride and maleic acid in pesticide products.

"Maleic anhydride and maleic acid are not persistent in the environment and are not expected to bioaccumulate in food webs. In the presence of water, maleic anhydride rapidly hydrolyzes to form maleic acid. The half-life of the hydrolysis of maleic anhydride to maleic acid in water at 25°C has been determined to be approximately 22 seconds. The half-life of maleic anhydride in air is estimated to be 4.2 to 18.6 hours (the estimated rate constants range from 4.3×10^{-11} to 4.9×10^{-17} cm^3 $molecule^{-1}$ sec^{-1}), due primarily to direct reactions with photochemically generated hydroxyl radicals. For maleic acid, the half-life in air is estimated to be 1.346 and 1.205 days for the cis- and trans- isomers, respectively.

Maleic anhydride and maleic acid are readily biodegraded under aerobic conditions in sewage sludge, and are expected to biodegrade in soil and water as well. Fugacity-based fate and transport modelling suggest that maleic anhydride, hydrolyzed to maleic acid in water and under humid conditions, will partition primarily to water. Level

III fugacity modelling indicates water as the primary compartment for distribution (air 0.3%, water 59%, soil 40.6%, sediment 0.02%)."

VI. Exposure Assessment

Maleic anhydride and maleic acid are used as stabilizers in pesticide formulations. The current tolerance exemption under 40 CFR 180.920 significantly limits the use of maleic anhydride and maleic acid to applications on apples with a minimum preharvest interval of 21 days. This limitation reduces the likelihood of residues on food. The physical/chemical properties and fate of maleic anhydride and maleic acid also limit the likelihood of residues on food, and contributions to drinking water are not expected. Maleic anhydride is rapidly hydrolyzed to maleic acid in most environments, and both chemicals degrade in the atmosphere and are expected to biodegrade in soil and water. Bioaccumulation in the food web is not expected.

In the absence of actual dietary exposure data for maleic anhydride and maleic acid, a chronic dietary exposure analysis was performed based on a screening level dietary assessment that assumed residues of maleic anhydride and maleic acid in apple commodities equivalent to the highest established active ingredient tolerance level residues for those commodities and 100% crop treated Even with these highly conservative assumptions, the risk estimates are well below the Agency's level of concern. Using the above-noted conservative exposure assumptions, EPA has concluded that exposure to maleic anhydride and maleic acid from food and drinking water will utilize approximately 12% of the IRIS oral RfD (0.1 mg/kg/day) for the U.S. population, and 86% of the IRIS oral RfD (0.1 mg/kgs/day) for non-nursing infants, the most highly exposed population subgroup.

Considering their physical/chemical and fate properties and the limited use on apples as well as the highly conservative dietary exposure assessment described above, dietary exposures of concern from food and drinking water are not expected from the use of maleic anhydride and maleic acid as inert ingredients in pesticide formulations. For the same reasons, dermal and inhalation exposures of concern from residential uses (home apple trees) are not anticipated.

Considering their physical/chemical and fate properties and the limited use on apples, dietary exposures of concern from food and drinking water are not expected from the use of maleic anhydride and maleic acid as inert ingredients in pesticide formulations. For the same reasons, dermal and inhalation exposures of concern from residential uses (home apple trees) are not anticipated.

VII. Aggregate Exposures

In examining aggregate exposure, the FFDCA section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other nonoccupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

For maleic anhydride and maleic acid, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate given the lack of human health concerns associated with the low levels of exposure to these chemicals when used as inert ingredients in pesticide formulations.

VIII. Cumulative Exposure

Section 408(b)(2)(D)(v) of 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."

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 maleic anhydride or maleic acid and any other substances and, these materials do not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that maleic anhydride and maleic acid have 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/.

IX. Human Health Risk Characterization

Maleic anhydride and maleic acid are used as inert ingredient stabilizers in pesticide formulations. Their use under 40 CFR 180.920 is significantly limited to applications on apples, with a minimum pre-harvest interval of 21 days.

Available toxicological data indicate the relatively low acute toxicity of maleic anhydride and maleic acid by the oral and dermal routes of exposure. However, severe eye and skin irritation have been reported in animal studies. Maleic anhydride has also been shown to be a skin sensitizer and possible respiratory sensitizer. Maleic acid is not predicted to be either a skin or respiratory sensitizer. Subchronic and chronic toxicity studies indicate that respiratory tract and eye irritation are likely following repeated exposure to maleic anhydride and maleic acid. In a multi-generation rat reproductive study, the LOAEL for parental effects (mortality, body weight changes, and respiratory irritation) was 20 mg/kg/day but no adverse effects on litter size and on pup survival were noted at doses up to 150 mg/kg/day (OECD SIAP, 2004; HSDB, 2006). In a 2-year chronic study, male and female rats were fed 0, 10, 32, or 100 mg/kg/day for 2 years. No kidney effects were observed and the NOAEL of 10 mg/kg/day was determined for the mild effect of slight to marginal decreases in body weight that were observed at 32 and 100 mg/kg/day (OECD SIAP, 2004; U.S. EPA, 2006b). No reproductive or developmental effects from exposure to maleic anhydride or maleic acid have been reported in animal studies at doses up to 140 mg/kg/day. No neurotoxicity has been observed and no treatment-related reproductive or developmental effects are reported. Negative results for maleic acid can be inferred from the

rapid hydrolysis of maleic anhydride to maleic acid. Maleic anhydride and maleic acid are also negative for genotoxicity.

Maleic acid and maleic anhydride exhibit a relatively low order of toxicity for human health effects. In addition to low toxicity, the potential for exposure is quite limited. The use of the chemicals as inert ingredients is limited to use on apples with a minimum pre-harvest interval of 21 days. Considering their physical/chemical and fate properties and the significant limitations on use, dietary exposures of concern from food and drinking water are not expected from the use of maleic anhydride and maleic acid as inert ingredients in pesticide formulations. For the same reasons, dermal and inhalation exposures of concern from residential uses (home apple trees) are not anticipated.

Taking into consideration all available information on maleic anhydride and maleic acid, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to maleic anhydride and maleic acid when considering dietary exposure (through food commodities and drinking water) and all other non-occupational sources for which there is reliable information. Therefore, it is recommended that the one exemption from the requirement of a tolerance established for residues of maleic anhydride and maleic acid under 40 CFR 180.920, when used in pesticide formulations applied to apples with a minimum pre-harvest interval of 21 days, can be considered reassessed as safe under section 408(q) of the FFDCA.

X. Ecotoxicity and Ecological Risk Characterization

The following is taken directly from EPA's report submitted to OECD under the SIDS High Production Volume Chemicals Program (OECD SIAP, 2004). This information indicates low toxicity to aquatic fish, aquatic invertebrates, and algae.

> "Acute aquatic toxicity testing indicates a low order of toxicity when the effect of pH is taken into consideration. Acute values were 96-hour LC_{50} in fish – 75 mg/L and 48-hour EC50 in daphnids – 330 mg/L (in non-neutralized conditions, pH 2-3). In a study which took pH into consideration, the 24-hour daphnid EC_{50} was 88, 83, and 5600 mg/liter for non-neutralized maleic anhydride, non-neutralized maleic acid, and neutralized maleic anhydride, respectively. This supports the observation that pH may be a significant confounder in the observed aquatic toxicity of maleic anhydride/maleic acid.
>
> The 72-hour algae NOEC of 130 mg/L (measured as maleic acid in neutralized conditions and the highest dose tested). The combination of low aquatic toxicity, low log Pow and readily biodegradability suggest no significant hazard of long-term effects in the aquatic environment."
>
> "Maleic anhydride and maleic acid are not persistent in the environment and are not expected to bioaccumulate in food webs."

Based on the ecotoxicity information taken directly from the OECD SIAP (2004), both maleic anhydride and maleic acid are categorized as "Slightly toxic" to freshwater fishes based on an LC_{50} value of 75 mg/L and a acidic pH range of 2-3.

Based on the ecotoxicity data in Agency's ECOTOX Database, maleic anhydride is categorized as "Practically Non-toxic" to freshwater fish with LC_{50} values ranging from 115,000 to 260,000 µg/L. Maleic acid is categorized as "Practically Non-Toxic" to freshwater fishes with LC50 values ranging from 5,000 to >300,000 µg/L.

While the Agency's Ecotox Database did not contain any chronic toxicity data for freshwater fishes for either inert, both chemicals are expected to display similar toxicity to freshwater fish from a chronic standpoint.

Tables 1 and 2 display the toxicity values for both Maleic Anhydride and Maleic Acid in reference to freshwater fishes on an acute toxicity basis.

Table 1- Toxicity Of Maleic Anhydride to Freshwater Fishes

SPECIES	TOXICITY VALUE (ppb)	TOXICITY CATEGORY	REFERENCE NUMBER
Silver fish (*Leuciscus idus*)	LC_{50}= 115,000	Practically non-toxic	715
Bluegill sunfish (*Lepomis macrochirus*)	LC_{50}= 138,000	Practically non-toxic	715
Rainbow trout (*Oncorhynchus mykiss*)	LC_{50}= 165,000	Practically non-toxic	719
Western mosquitofish (*Gambusia affinis*)	LC_{50}= 180,000	Practically non-toxic	719
Western mosquitofish (*Gambusia affinis*)	LC_{50}= 230,000-240,000	Practically non-toxic	5940
Rainbow trout (*Oncorhynchus mykiss*)	LC_{50}= 260,000	Practically non-toxic	12448

Table 2- Toxicity of Maleic Acid to Freshwater Fishes

SPECIES	TOXICITY VALUE (ppb)	TOXICITY CATEGORY	REFERENCE NUMBER
Fathead minnow (*Pimephales promelas*))	LC_{50}= 5,000	Practically non-toxic	715
Silver fish (*Leuciscus idus*)	LC_{50}= 106,000	Practically non-toxic	715
Green sunfish (*Lepomis cyanellus*)	LC_{50}= 20,000-40,000	Practically non-toxic	719
Bluegill sunfish (*Lepomis macrochirus*)	LC_{50}= >300,000	Practically non-toxic	719

While neither the OECD SIAP (2004) nor the Agency's ECOTOX Database contained any ecotoxicity effects data for these two inert ingredients in reference to estuarine/marine fishes, both maleic anhydride and maleic acid are expected to exhibit similar toxicity to estuarine/marine fishes as they do to freshwater fishes. Therefore, both maleic anhydride and maleic acid are expected to be categorized as "Practically Non-toxic" to estuarine/marine fishes on an acute toxicity basis.

Based on the ecotoxicity data reported in the Agency's ECOTOX database, both maleic anhydride and maleic acid are categorized as practically non-toxic to freshwater invertebrates on an acute toxicity basis. For maleic anhydride the freshwater invertebrate EC_{50} value was 560,000 ppb while the freshwater invertebrate EC_{50} value for maleic acid was 160,000 ppb. Thus, maleic anhydride and maleic acid are categorized as practically non-toxic to freshwater invertebrates on an acute toxicity basis.

Since the Agency's ECOTOX database did not contain any data concerning the chronic toxicity effects toward freshwater invertebrates, both inert ingredients are expected to exhibit similar toxicity on chronic toxicity basis to freshwater invertebrates as they do on an acute toxicity basis.

While neither the OECD SIAP (2004) nor the Agency's ECOTOX Database contained any ecotoxicity effects data for these two inert ingredients in reference to estuarine/marine invertebrates, both maleic anhydride and maleic acid are expected to exhibit similar toxicity to estuarine/marine invertebrates as they do to freshwater invertebrates. Therefore, both maleic anhydride and maleic acid are expected to be categorized as "Practically Non-toxic" to estuarine/marine invertebrates on an acute toxicity basis.

Tables 3 and 4 below depict the toxicity effects of both maleic anhydride and maleic acid toward freshwater invertebrates.

Table 3-Maleic Anhydride toxicity to Freshwater invertebrates

Species	Toxicity Value (ppb)	Toxicity Category	Ecotox Database Reference Number
Water flea (*Daphnia magna*)	EC_{50}= 560,000	Practically non-toxic	16475

Table 4-Maleic Acid Toxicity To Freshwater Invertebrates

Species	Toxicity Value (ppb)	Toxicity Category	Ecotox Database Reference Number
Water flea (*Daphnia magna*)	EC_{50}= 160,000	Practically non-toxic	16474

Considering the physical properties of the compound, aquatic exposures are possible. Acute effects to aquatic species (listed and non-listed) are likely if application rates exceed more than one-hundred pounds per acre. Chronic effects are largely unknown. Terrestrial risks are likely to be lower than for aquatic species based on available mammalian data used as a surrogate for other terrestrial phase animals.

Based on the toxicity exhibit toward mammals for maleic anhydride and maleic acid with oral LD_{50} toxicity values ranging from 390-1050 mg/kg, both maleic anhydride and maleic acid are categorized as "Moderately toxic to Practically non-toxic to mammals. Using this as a surrogate for avian species, both maleic anhydride and maleic acid may have a similar toxicity classification for birds.

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