



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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

September 22, 2005

MEMORANDUM

FROM: Susan Lewis, Chief
Reregistration Branch 1
Special Review and Reregistration Division (SRRD)

TO: Debra Edwards, Director
Special Review and Reregistration Division (SRRD)

SUBJECT: Tolerance Reassessment Eligibility Decision on Maleic Hydrazide

This memorandum is to inform you that the tolerances for the active ingredient maleic hydrazide will be maintained at current levels. There are currently three tolerances established for the residues of maleic hydrazide - two established under 40 CFR §180.175(a)(1) and one established under §180.175(a)(2). As a result of the Agency's determination that these tolerances should be maintained, the current tolerances of maleic hydrazide are considered reassessed.



United States Office of Prevention, Pesticides
Environmental Protection and Toxic Substances
Agency (7508C)

September 22, 2005

Report of the Food Quality Protection Act (FQPA) Tolerance Reassessment Progress and Risk Management Decision (TRED) for Maleic Hydrazide



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This is the Environmental Protection Agency's (hereafter referred to as EPA or the Agency) "Report of the Food Quality Protection Act (FQPA) Tolerance Reassessment Progress and Risk Management Decision for Maleic Hydrazide," which was approved on September 22, 2005. This document is also known as a Tolerance Reassessment Decision, or TRED. A Notice of Availability of this tolerance reassessment decision will be published in the near future.

The Federal Food, Drug and Cosmetic Act (FFDCA), as amended by FQPA, requires EPA to reassess all the tolerances for registered chemicals in effect on or before the enactment of the FQPA on August 3, 1996. In reassessing these tolerances, the Agency must consider, among other things, aggregate risks from non-occupational sources of pesticide exposure, whether there is increased susceptibility to infants and children, and the cumulative effects of pesticides with a common mechanism of toxicity. Once a safety finding has been made, the tolerances are considered reassessed. Existing tolerances and exemptions associated with maleic hydrazide must be reassessed in accordance with FFDCA, as amended by FQPA.

The term "maleic hydrazide" in this document refers to both the technical acid and the potassium salt of maleic hydrazide. Maleic hydrazide (1, 2-dihydro-3,6-pyridinedione) is a plant growth regulator and herbicide. It is used as a plant growth regulator to control sucker growth on tobacco, to retard the growth of turf, and to inhibit sprout growth in stored onions and potatoes, as well as on non-bearing apple and citrus trees, forest trees, and ornamental plants. Maleic hydrazide is used as a herbicide to control quack grass, wild onions, wild garlic, and other undesirable weeds on residential lawns, in terrestrial non-food crops and industrial areas, and along roadsides and other rights-of-way. The application of maleic hydrazide is limited to professional applicators only, and the only residential exposures expected to occur are after the application to turf.

The Agency has completed the human health risk assessment of maleic hydrazide for purposes of issuing a Tolerance Reassessment Eligibility Decision (TRED). These findings are presented fully in the document, "*Maleic Hydrazide HED Risk Assessment for Tolerance Reassessment Eligibility Decision (TRED) Document*," dated September 2, 2005. The toxicological database for maleic hydrazide is adequate for hazard characterization and sufficient data are available to assess potential susceptibility to the young. There is a low degree of concern for the quantitative or qualitative susceptibility effects noticed in animal studies and there are no residual uncertainties for the pre-and postnatal effects; therefore, the special FQPA Safety Factor was reduced to 1X.

Technical grade maleic hydrazide contains hydrazine as a contaminant. Since hydrazine has been associated with tumor induction, the Agency established and maintained an upper limit for hydrazine at 15 ppm in technical maleic hydrazide products in 1982. This was a level determined not to cause concern based on the calculations of lifetime carcinogenicity risks to humans. The carcinogenic potential of maleic hydrazide *per se* was classified into “Group E” – evidence of non-carcinogenicity for humans.

Maleic hydrazide has a low acute toxicity (Category IV) by oral, dermal, and inhalation routes of exposure. It is not a skin or eye irritant, nor is it a skin sensitizer.

An acute dietary/drinking water assessment was not conducted because no effect attributable to a single dietary exposure was observed in animal studies. A Tier 1 chronic aggregate (food + water) assessment was conducted, based on a NOAEL of 25 mg/kg/day from a chronic toxicity/carcinogenicity study, which showed decreased body weight in rats at the LOAEL of 500 mg/kg/day. Because no monitoring data are available for maleic hydrazide in surface or ground water, EPA used models to estimate Estimated Drinking Water Concentrations (EDWCs). The peak EDWC for surface water is 500 µ/L, and the annual average EDWC is 3.46 µ/L. The peak and annual average EDWCs for ground water are both 0.011 µ/L. Using the DEEM model, chronic aggregate dietary exposures were estimated to be 52% of the cPAD, and are below the Agency’s level of concern.

The only residential exposure scenario assessed for maleic hydrazide is incidental oral exposure following turf treatment by professional applicators. Dermal exposure is not a pathway of concern, based on the results of the dermal toxicity study in rats, and thus, dermal exposures following professional applications to turf were not assessed. The residential assessment was done based on the incidental oral NOAEL of 29 mg/kg/day from a chronic dog study, in which decreased body weight gain and reduced heart weight were observed at the LOAEL of 87 mg/kg/day (males) and 105 mg/kg/day (females). An aggregate MOE of 200 was calculated for this exposure scenario, to account for oral exposure through hand to mouth contact, object to mouth contact, and soil ingestion. This MOE is greater than the target MOE of 100, and thus indicates no risk concern.

A short-term aggregate risk assessment was conducted, which estimated risk associated with combined risks from average food and drinking water exposures and short-term incidental oral exposures in residential settings. This assessment indicates that the short-term aggregate MOE is 102, and therefore not of concern (target MOE = 100).

Tolerances have been established under 40 CFR §180.175(a)(1) for residues of the parent compound maleic hydrazide (1,2-dihydro-3,6-pyridazinedione) in/on onions and potatoes at 15.0 ppm and 50.0 ppm, respectively. Additionally, a tolerance for potato chips at 160 ppm is established under §180.175(a)(2). These tolerances will be maintained. An aggregate assessment was conducted for exposures through food, drinking water, and residential applications of maleic hydrazide, and the Agency has determined that the human health risks from these combined exposures are within acceptable levels. In other words, EPA has concluded

that the tolerances for maleic hydrazide meet FQPA safety standards, and are considered reassessed.

In addition, based on available residue data, EPA plans to establish a new tolerance for potato granules at 200 ppm. Tolerances for livestock commodities may also be required following the review of additional data requested by the Agency. The qualitative nature of the residues in plants is adequately understood. The residue of concern in plants is maleic hydrazide per se and in livestock is maleic hydrazide (free and conjugated) and 3-pyridazinone (T. Morton, D317484, 8/05). The metabolite 3-pyridazinone is not expected to be of greater toxicity than the parent based on structural similarity to maleic hydrazide.

Although the database is sufficient to make a tolerance reassessment determination for maleic hydrazide, there are still several outstanding data gaps that must be fulfilled. The Agency is requiring data on the magnitude of residue in livestock. Simulated feeding studies using [¹⁴C]maleic hydrazide indicate that detectable residues occur in livestock and that tolerances are needed for livestock commodities. Feeding studies for ruminants must be conducted using analytical methodology specific for residues of concern. In addition, storage stability studies for onions and potatoes are being required. Storage stability trials for potatoes and onions raw agricultural commodities were only carried out to 6 months, which does not cover the length of time the samples were stored prior to analysis. In addition, a 28-day inhalation toxicity study is currently a data gap, and is therefore being required.

EPA is also requiring a couple of changes to the maleic hydrazide product labels. A statement will be required on all labels restricting application to professional applicators only. In addition, a 120-day plant-back interval will be required for all rotational crops.

FQPA requires that EPA consider “available information” concerning the cumulative effects of a particular pesticide’s residues and “other substances that have a common mechanism of toxicity.” The Agency considers other substances because low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect, as would a higher level of exposure to any of the substances individually. Risks summarized in this document are those that result only from the use of maleic hydrazide. The Food Quality Protection Act (FQPA) requires that 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 hydrazide and any other substances. In addition, Maleic hydrazide does not appear to produce a toxic metabolite produced by other substances which have tolerances in the U.S.

EPA is required under the FFDCA as amended by FQPA, to develop a screening program to determine whether certain substances “may have an effect in humans that is similar to endocrine effects.” In the available toxicity studies on maleic hydrazide, there was no estrogen or androgen mediated toxicity. Thyroid effects in the presence of liver toxicity were seen in both

sexes at the highest dose tested in the chronic dog study. When additional appropriate screening and/or testing protocols being considered under the Agency’s Endocrine Disruption Screening Program (EDSP) have been developed, maleic hydrazide may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

This document summarizes the Agency’s decision on the tolerance reassessment for maleic hydrazide. Any questions regarding this decision should be directed to the Chemical Review Manager for maleic hydrazide, John Pates, Jr. at (703) 308-8195 or pates.john@epa.gov.

Tolerance Reassessment Summary for Maleic Hydrazide			
Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comments/ <i>Correct Commodity Definition</i>
Tolerances under 180.175(a)(1)			
Onions, dry bulb	15.0	15.0	<i>Onions, dry bulb</i>
Potatoes	50.0	50.0	<i>Potato</i>
Tolerance under 180.175(a)(2)			
Potato chips	160	160	<i>Potato, chips</i>
Potato, granules	None	200	New tolerance needed. <i>Potato, granules/flakes</i>
Tolerance Under Consideration			
Meat and milk	N/A	TBD	A ruminant feeding study is required in order to set these tolerances