

the processed food itself is treated or comes in contact with a pesticide.

If a food additive regulation must be established, section 409 of the FFDCA requires that the use of the pesticide will be "safe" (21 U.S.C. 348(c)(3)). Relevant factors in this safety determination include: (1) the probable consumption of the pesticide or its metabolites; (2) the cumulative effect of the pesticide in the diet of man or animals, taking into account any related substances in the diet; and (3) appropriate safety factors to relate the animal data to the human risk evaluation. Section 409 also contains the Delaney clause, which specifically provides that, with little exception, "no additive shall be deemed safe if it has been found to induce cancer when ingested by man or animal" (21 U.S.C. 348(c)(3)).

Before a pesticide may be sold or distributed, it must be registered under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). To qualify for registration, a pesticide must, among other things, perform its intended function without causing "unreasonable adverse effects on the environment" (7 U.S.C. 136a(c)(5)). The term "unreasonable adverse effects on the environment" is defined as "any unreasonable risk to man or the environment taking into account the economic, social and environmental costs and benefits of the use of any pesticide" (7 U.S.C. 136(bb)).

#### B. Regulatory Background

On May 25, 1989, the State of California, the Natural Resources Defense Council, Public Citizen, the AFL-CIO, and several individuals filed a petition requesting that EPA revoke several food additive regulations and challenging EPA's de minimis interpretation of the Delaney clause. The petition, which sought a "zero-risk" interpretation of the Delaney clause, requested that EPA revoke certain food additive regulations. The petitioners argued that these food additive regulations should be revoked because they violate the Delaney clause.

EPA responded to the petition by revoking certain food additive regulations, but retained several others on the grounds that the Delaney clause provides an exception for pesticide residues posing de minimis risk; EPA denied the petition for the food additive regulations determined to fall under this exception.

EPA's response was challenged by the petitioners in the U.S. Court of Appeals, Ninth Circuit. On July 8, 1992, the court ruled in *Les v. Reilly*, 968 F.2d 985 (9th Cir.), cert. denied, 113 S.Ct. 1361 (1993),

that the Delaney clause barred the establishment of a food additive regulation for pesticides which "induce cancer" no matter how infinitesimal the risk.

On July 14, 1993, EPA issued a revised response to the petition taking into account the court's ruling. That revised response granted the original petition and revoked the food additive regulations named in the petition. The food additive regulations for two of the four affected pesticides, benomyl and trifluralin, have been reinstated pending judicial review by the Court of Appeals, District of Columbia Circuit, of several registrants' challenge to the revocation.

In implementing the court's decision in *Les v. Reilly*, EPA has taken steps to identify and revoke all section 409 tolerances for pesticides which have been found to "induce cancer." EPA has issued two lists of pesticide uses which would likely be affected by the court's decision. The first list contains affected food and feed additive regulations, and the second identifies uses for pesticides that have either been found to induce cancer or are likely to be so classified where data show a food or feed additive regulation needs to be established. Both lists have been updated to reflect changes in data reviews and other regulatory actions (see 59 FR 14980, March 30, 1994). The first proposed revocation, which included 26 food additive regulations for seven pesticides classified as "B", probable human carcinogens or "C", possible human carcinogens subject to quantification by a linear low-dose extrapolation model, was published in the **Federal Register** of July 1, 1994 (59 FR 33941).

#### II. Proposed Revocation of Section 409 Tolerances Which are Inconsistent with the Delaney Clause

EPA intends to revoke all food and feed additive regulations which are inconsistent with the Delaney clause. This notice proposes revocation of all food additive regulations published in the March 30, 1994 **Federal Register** notice which have not previously been proposed for revocation. EPA expects to publish additional proposed revocations for feed additive regulations in the near future.

##### A. Basis for Proposing Revocation

As a result of the court's 1992 decision, the only issue to be considered for these proposed revocations is whether acephate, triadimefon, imazalil, and iprodione qualify under the Delaney clause as having been "found to induce cancer when ingested by man or animals, or it is found, after tests which are appropriate for the evaluation of the

safety of food additives, to induce cancer in man or animal." 21 U.S.C. 348(c)(3)(A). If EPA finds they are human or animal carcinogens within the meaning of the Delaney clause, the food additive regulations must be revoked.

In construing the "induce cancer" standard as to animals, EPA follows a weight-of-the-evidence approach which is guided, where appropriate, by the principles in EPA's Cancer Assessment Guidelines. In regard to animal carcinogenicity, EPA, in general, interprets "induces cancer" to mean:

The carcinogenicity of a substance in animals is established when administration in adequately designed and conducted study or studies results in an increase in the incidence of one or more types of malignant (or, where appropriate, benign or a combination of benign and malignant) neoplasms in treated animals compared to untreated animals maintained under identical conditions except for exposure to the test compound. Determination that the incidence of neoplasms increases as the result of exposure to the test compound requires a full biological, pathological, and statistical evaluation. Statistics assist in evaluating the biological significance of the observed responses, but a conclusion on carcinogenicity is not determined on the basis of statistics alone. Under this approach, a substance may be found to "induce cancer" in animals despite the fact that increased tumor incidence occurs only at high doses, or that only benign tumors occur, and despite negative results in other animal feeding studies. (See 58 FR 37863, July 14, 1993; 53 FR 41108, October 19, 1988; and 52 FR 49577, December 31, 1987).

Acephate, triadimefon, imazalil, and iprodione all qualify as animal carcinogens under this test.

Summarized below is the information supporting EPA's determination that these pesticides "induce cancer." Full copies of each of these reviews and other references in this notice are available in the OPP Docket, the location of which is given under "ADDRESSES" above.

##### Acephate

After a full evaluation of all the data and supporting information regarding animal carcinogenicity, EPA has concluded that exposure to acephate results in the induction of malignant hepatocellular carcinomas in female CD-1 mice.

Male and female CD-1 mice were fed 0, 50, 250, or 1,000 parts per million (ppm) of acephate for 105 weeks. Although fewer low-dose and mid-dose female mice survived to the end of the study compared with controls, the survival of the highest dose tested (HDT) female mice and all male mice was higher than that with the controls. Decreases in body weight gain ranged