

**§ 225.5 Provisions of agreement.**

Each trade agreement entered into by an airline hereunder shall provide:

( ) That it shall become effective on a specified day, on or before January 1, 1976:

**3. Amend § 225.6 to read as follows:****§ 225.6 Limitation on total value of trade agreements.**

The total value of trade agreements entered into by any single airline in accordance with the provisions of this part shall be limited, in the aggregate, to the following:

(a) For the airlines identified in § 225.1(a)(3), \$200,000;

(b) For the airlines identified in § 225.1(a)(4) which have gross transport operating revenues of less than \$2 million in the year prior to the effective date of the agreement in question, \$20,000 each year;

(c) For the airlines identified in § 225.1(a)(4) which have gross transport operating revenues of \$2 million or more in the year prior to the effective date of the agreement in question, \$50,000 each year;

(d) For the airlines identified in § 225.1(a)(6), \$100,000 each year;

(e) For the airlines identified in § 225.1(a)(1):

(1) \$50,000 plus \$4,000 per station operated on January 1, 1972, for agreements becoming effective during 1972.

(2) \$4,000 per subsidy-eligible station operated on January 1, 1973, in Class Rate VI station classifications C, D, and E, for agreements becoming effective during 1973.

(3) \$4,000 per subsidy-eligible station operated on January 1, 1974, in Class Rate VI station classifications D and E, for agreements becoming effective during 1974.

(4) \$4,000 per subsidy-eligible station operated on January 1, 1975, in Class VI station classification E, for agreements becoming effective on and after January 1, 1975.

[FR Dec 72-15964 Filed 9-19-72; 9:51 am]

## ENVIRONMENTAL PROTECTION AGENCY

[40 CFR Part 180]

### PESTICIDE CHEMICAL SAFETY

#### Proposed Toxicology Guidelines

A. Pesticide petitioners have raised questions about the kinds of data and other information which will satisfy the toxicology requirements of the pesticide procedural and interpretative regulations. Accordingly, it has been concluded that guidelines for studies to meet such requirements should be officially published to eliminate this uncertainty.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 701(a), 52 Stat. 1055; 21 U.S.C. 371(a)) and the authority transferred to

the Administrator of the Environmental Protection Agency (35 F.R. 15623), and the authority delegated by the Administrator to the Deputy Assistant Administrator for Pesticides Programs (36 F.R. 9038), it is proposed that Part 180 be amended by adding the following new section to Subpart B:

#### § 180.36 Toxicology guidelines for evaluating pesticide chemical safety of residue tolerances.

(a) The following guidelines summarize in detail for the petitioner the Agency's toxicological data requirements for pesticide petitions. To determine the safety of a pesticidal chemical to whose toxic effects man or animals are exposed when that chemical is added directly or indirectly to food, the Agency will consider all relevant factors, including:

(1) Available toxicological data reflecting experimental studies in animals and controlled studies in man.

(2) Epidemiological data on effects from general exposures to the pesticide.

(3) Estimated average daily intake of the pesticide by those whose diet normally includes foods containing such pesticides.

(4) Adequacy of the safety factor with reference to severity of toxicity obtained by dividing the quantity of the substance that produces no effect in the most sensitive laboratory animal tested by the quantity of the substance expected in the diet of man on a mg./kg. daily, body weight basis.

(b) The toxicological investigation of a substance proposed for pesticide use may be conducted as outlined in the following sections. Where strong or alarming biological effects in the test animals are observed, it may be necessary to do animal studies in addition to those specifically prescribed before any use of the substance will be permitted. Safety evaluation studies must be done under the guidance of qualified scientists who by training and experience can plan and employ reasonable experimental procedures to adequately explore unforeseen toxicological manifestations. Nothing in this guideline shall be construed as relieving the investigator of this responsibility.

(c) The toxicological data requirements for pesticidal chemicals are dependent upon the proposed use patterns for the specific chemical. The toxicity and impact upon other organisms in the environment must also be considered in the evaluation of the chemical. As protocols for such evaluations become available, they should be included in the testing programs.

(d) Limited use of a specific chemical may modify the data requirements. In specified instances, a temporary tolerance is granted to permit experimental pesticide field trials on a limited scale in accordance with a temporary permit. In these instances, for nonnegligible residues, a progress report on the lifespan feeding studies at approximately 1 year and the reproduction studies through the first generation will suffice.

(e) The pesticide used for toxicological testing should be the same chemically

characterized technical product used and produced commercially. Test diets should be analyzed at intervals to check for stability of test substances.

(f) If plant residue studies show that a significant portion of the residue is a metabolite or degradation product of the parent compound, then acute toxicity (and in some instances subacute toxicity studies) for such a product will be required.

(g) Protocols should be designed so that the data can be evaluated statistically.

#### GUIDELINES

##### A. Toxicological data for all tolerances:

1. *Acute toxicity*—a. *Oral administration*. Oral LD<sub>50</sub> in at least two species of laboratory animals. A full and complete description of effects observed should be reported.

b. *Neurotoxicity*. Neurotoxicity test for cholinesterase inhibitors.

1. *Species—Chickens*. Although phosphorus compounds have been shown to produce locomotor ataxia in some animals other than chickens, the observations in hens of this species are usually more clear cut.

ii. *Procedure*. Single oral dose at LD<sub>50</sub> level to be administered to hens over 9 months of age and the birds observed for 21 days. If no response, re-dose and observe another 21 days. Include negative and positive controls (TOCP, 500 mg./kg. orally).

c. *Observations*. The absence of clinical neurotoxic effects in birds surviving two LD<sub>50</sub> doses of the compound at an interval of 3 weeks will be accepted as evidence that the compound probably has no neurotoxic potential. Selected nervous tissue of any birds showing doubtful responses should be examined, as well as positive controls.

2. *Subacute toxicity*. Oral exposure (direct dosing or in the diet).

a. *Number of species*. At least two species, one a nonrodent.

b. *Number of animals*. At least 15 of each sex at each dosage level for rodents. For non-rodents, four of each sex per level.

c. *Duration—Ninety days*. For the non-rodent (usually dogs), the study can be extended to 6 months and histopathological examination made at the end of that period instead of 3 months. (See B.3.c. under Non-rodent studies (long-term)).

d. *Dosage*. At least three dosage levels plus a control group. One dosage level should manifest severe pharmacological effects and one level should be "no-effect".

e. *Observations*. Growth, food consumption, general appearance, signs of local and systemic toxicity, mortality, hematology, urinalysis, organ function tests (SAP, blood sugar, urea, etc.), organ weights, and gross and microscopic pathology. Tissues examined should be those described in the WHO Technical Report Series No. 426 (1969). Eyes should be examined both ante and post mortem. All animals dying before termination should be examined grossly and microscopically.

1. *Rodents*. All tissues from a representative number of rodents from the highest dosage level and the controls should be examined histopathologically, as well as major organs from each of the lower dosage levels. All gross lesions should be examined.

ii. *Nonrodents*. All tissues from every nonrodent at all levels should be examined.

1. Atropine or PAM may be used to insure survival of sufficient hens.

1. Guidelines for a uniform reporting of pathological examinations are being prepared and will be made available when completed.

1. *Cholinesterase inhibition.* If the test compound is an organophosphate or carbamate pesticide, measurement of cholinesterase inhibition of plasma and red cells at appropriate intervals and of brain at termination is required.

3. *Negligible residue tolerances.* The completion of the acute and subacute toxicity studies are required for negligible residue tolerances for pesticide chemicals. The "negligible residue" concept defined in 40 CFR 180.1(1) as adding to the diet an amount of pesticide chemical which will be less than 1/2000 the amount demonstrated to have no effect from at least two 90-day feeding studies cannot be construed literally in all cases. A negligible level should refer to a residue that is toxicologically insignificant and usually about 0.1 p.p.m. or less on raw agricultural commodities for human consumption.

B. Toxicological data for nonnegligible tolerances:

1. See A. (Toxicological data for all tolerances.)

2. *Carcinogenicity studies (long-term)*—a. *Species.* Usually two rodents.

b. *Selection of animals.* Weanling random-bred animals. At the option of the experimenter, these animals may be derived from a normal stock colony and maintained on the test diet for their lifespan or they may be the  $F_1$  progeny from a reproduction study in which the parents have been treated with the pesticide.

c. *Dosage.* At least three dosage levels plus a control; the highest dosage should elicit any specific pharmacological action the test compound might have. One dose level should show no observable differences from control animals.

d. *Duration.* Two years for rats and hamsters, 18 months for mice.

e. *Number of animals.* The groups should be large enough to assure an adequate number of survivors at the end of the study. Depending upon the strain of rodent, from 25-50 animals of each sex per dose level is suggested.

f. *Observations.* 1. Growth, food consumption, general appearance, signs of local and systemic toxicity, terminal organ weights, and gross and histopathological examination of both rodent species.<sup>1</sup>

ii. In one species (usually the rat), clinical laboratory tests should be performed at 3, 6, 12, 18, and 24 months. These should include routine hematological measurements, qualitative urinalysis, cholinesterase activity at intervals on plasma and red cells and terminally in the brain to determine "no-effect" level (in the case of carbamate and organophosphate pesticides), alkaline phosphatase determination (other serum enzymes if indicated such as SGOT), and organic blood constituent analysis (Ca, Cl, Na, K if indicated).

3. *Nonrodent studies (long-term)*—a. *Species.* Dogs, monkeys, and swine.

b. *Route.* Orally.

c. *Duration—Six months.* This may be accomplished by extending the 90-day subacute study until biochemical studies are completed.

d. *Dosage levels.* Three test plus a control.

e. *Number of animals.* Four of each sex at each level.

f. *Observations.* See under B.2.f. i, and ii.

4. *Reproduction study (long-term)*—a. *Species.* One mammalian species, usually one of the same rodent species used in the chronic toxicity test.

<sup>1</sup> Histopathological examination should be done on all survivors at the highest dosage level and controls and on major organs in 10 males and 10 females at the lower levels. Changes in organs at the highest dosage level should be looked for in the lower feeding levels. All gross lesions at all levels should be examined.

b. *Dosage levels.* Two dosage levels and a control. These levels may be derived from the 90-day study and should be (1) the lowest dose that caused a minimum effect and (2) one lower dose.

c. *Three successive generations.* One litter per generation is sufficient, provided the first litter in any generation is healthy.

d. *Observations.* Fertility index, viability index, survival to day four, weaning index, lactation index, body weights, and external abnormalities.

5. *Teratogenicity studies*—a. *Species.* Rat, mouse, hamster, rabbit, or monkey. If the rat is used for the reproduction study (B.4.), a different species should be used for this study.

b. *Number of animals.* Twenty pregnant female rodents per level, 10 pregnant female nonrodents per level.

c. *Dose levels.* Three levels plus a control, with levels selected so that a "no-effect" level will be ascertained even though an effect is found at the highest level.

d. *Route of administration.* Orally.

e. *Period of dosing.* Daily through the sensitive period of organogenesis. For example, days 6 through 15 for rats, days 6 through 10 for hamsters.

f. *Method of birth.* Except for monkeys, deliver fetuses by Caesarian section 1 day prior to term.

g. *Observations.* Number and position of resorption sites, number of corpora lutea and implantation sites, fetal weights, external malformations, and skeletal anomalies after clearing and staining with Alizarin red.

6. *Metabolism studies.* Metabolism studies are required. These may be radiotracer studies. One or two species should be studied, depending upon the use and the nature of the residue on the raw agricultural commodities.

7. *Mutagenicity studies.* If data from other toxicological tests indicate a mutagenic potential, then specific tests should be made. A survey of available methods indicates they are in an early developmental stage when applied to mammals. More data have been developed from the dominant lethal test, and this might be asked for if indicated.

8. *Special studies.* a. When appropriate, additional studies based upon similar chemical structure between the test compound and those (nitrophenolics, dioxins, etc.) known to produce specific toxic effects may be in order.

b. Proof of safety to livestock may be required if the tolerance requested is for non-negligible residues in livestock feed or from dermal application.

c. Studies may be required to demonstrate reversibility of effects found after subacute feeding.

Any omission of data or information suggested by the guidelines or substitution of other types of data or information should be accompanied by an explanation of why the material was omitted or how such substituted data adequately fulfill the requirements to demonstrate the safety of the requested clearance.

B. Due to the addition of certain sections to Subpart B and to provide for future such additions, it is proposed that the center heading immediately preceding § 180.29 be revised to read "Miscellaneous Provisions."

Interested persons may, within 30 days after publication hereof in the *Federal Register*, file with the Objections Clerk, Environmental Protection Agency, Room 3125, South Agriculture Building, 12th Street and Independence Avenue SW,

Washington, D.C. 20460, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof.

Dated: September 6, 1972.

WILLIAM M. UPWOLZ,  
Deputy Assistant Administrator  
for Pesticides Programs.

[FR Doc 72-15035 Filed 9-19-72; 8:47 am]

## FEDERAL COMMUNICATIONS COMMISSION

[47 CFR Part 1]

[Docket No. 19518]

### PUBLIC INTEREST GROUPS AS CONSULTANTS TO BROADCASTERS

#### Proposed Reimbursement for Legitimate and Prudent Expenses; Order Extending Time for Filing Comments and Reply Comments

In the matter of reimbursement for legitimate and prudent expenses of a public interest group for a consultancy to a broadcaster in certain instances.

1. The notice of inquiry and proposed rule making in the above-entitled proceeding, was adopted June 1, 1972, and published in the *Federal Register* on June 9, 1972, 37 FR 11592. Dates specified for filing comments and reply comments are September 11 and October 1, 1972, respectively.

2. On September 8, 1972, requests for extension of time for filing comments and reply comments were filed by Storer Broadcasting Co. (Storer) and by Black Earths for Soul in Television (BEST). The former requested an extension to and including September 14, 1972 and the latter to and including October 2, 1972. BEST supports its request by stating it is presently laboring under extraordinarily heavy workloads, and also that the press of end of summer schedules has set them back in work schedules. It further states that the extension is necessary to afford full and thoughtful considerations to the questions raised in this proceeding and to prepare intelligent comments.

3. We are of the view that the requested extension of time is warranted and would serve the public interest. Accordingly, it is ordered, That the time for filing comments in the above docket is extended to and including October 2, and to October 13, 1972, for the filing of reply comments.

4. This action is taken pursuant to authority found in sections 4(i), and 303(r) of the Communications Act of 1934, as amended, and § 0.281(d) (8) of the Commission's rules and regulations.

Adopted: September 12, 1972.

Released: September 13, 1972.

[SEAL] WALLACE E. JOHNSON,  
Chief, Broadcast Bureau.

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