Image 1

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

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

TXR NO. 0050633

**April 2, 2002**

**MEMORANDUM**

**SUBJECT:** ***IPROVALICARB*** - Report of the FQPA Safety Factor Committee.

**FROM:** Carol Christensen, Acting Executive Secretary
And
Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)

**THROUGH:** Ed Zager, Chairman
FQPA Safety Factor Committee
Health Effects Division (7509C)

**TO:** Alan Levy, Toxicologist
Registration Action Branch 2
Health Effects Division (7509C)

**PC Code: 098359**

The Health Effects Division (HED) FQPA Safety Factor Committee (SFC) met on March 11, 2002 to evaluate the hazard and exposure data for iprovalicarb with regard to making a decision on the additional safety factor for the protection of infants and children. The SFC recommended, based on reliable data, that no additional safety factor (1X) is necessary to protect the safety of infants and children in assessing iprovalicarb exposures and risks.

## I. HAZARD ASSESSMENT

(*Correspondence:* A. Levy to C. Christensen dated March 6, 2002)

1. Adequacy of the Toxicology Database

The Health Effect Division's Hazard Identification Assessment Review Committee (HIARC) met on January 31, 2002 to assess the hazards posed by this chemical. The HIARC concluded that the toxicological database for iprovalicarb is complete and adequate for FQPA assessment. There are developmental toxicity studies in two species, the rat and the rabbit, as well as a multi-generation study in the rat. There is no evidence of neurotoxicity or neuropathology in the hazard database. The HIARC determined that a developmental neurotoxicity study was not required for this chemical and no additional safety factors are needed to account for data deficiencies.

2. Determination of Susceptibility

There is no evidence for increased susceptibility of fetuses to *in utero* exposure of iprovalicarb in either the rat developmental or rabbit developmental studies. In both studies, the NOAELs for both maternal and developmental toxicity were the highest dose tested.

Based on the results in the 2-generation reproduction study in rats, a qualitative increased susceptibility of the neonates (as compared with adults) was demonstrated for Iprovalicarb. The parental systemic NOAELs were based on decreased body weights and increased liver weights as well as bile duct proliferation; for females, the parental systemic NOAELs were based on increased relative liver weights. Reproductive LOAELs were not attained (> HDT, LIMIT DOSE). In offspring, the NOAELs were based on decreased mean litter weight on day 28, reduced body weight during lactation, and increased pup relative liver weights as well as reduced lactation index in $F_1$. There was considered to be an increase in sensitivity of the neonates (as compared with adults) because of the lower lactation index (decreased pup survival) and decreased pup body weights.

3. Degree of Concern and Residual Uncertainties

Under the OPP 10X guidance, when evidence of increased susceptibility of the young is identified, the HIARC performs a Degree of Concern Analysis to: 1) determine the level of concern for the effects observed when considered in the context of all available toxicity data; and 2) identify any residual concerns after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment of this chemical. If residual concerns are identified, HIARC examines whether these residual concerns can be addressed by a special FQPA safety factor and, if so, the size of the factor needed. Since this chemical went to HIARC prior to implementation of the OPP 10X guidance, the



2

HED toxicology reviewer for iprovalicarb conducted the Degree of Concern Analysis, the results follow.

Although there is evidence for qualitative susceptibility in the 2-generation reproduction study, the toxicology reviewer concluded that there is a low level of concern (and no residual uncertainty) because: 1) the increased susceptibility (decrease in pup survival) was seen only at the highest dose tested (2074 mg/kg/day) which is twice the limit dose; 2) the decrease in pup survival was seen only in one generation ($F_1$, not replicated in $F_2$); 3) there are clearly defined NOAELs/LOAELs for parental and offspring toxicity; and 4) the effects seen in the offspring occurred at a much higher dose (192 mg/kg/day) than that used to establish the Chronic RfD (NOAEL of 2.62 mg/kg/day).

The FQPA SFC concluded that the data indicate there are no (residual) concerns for pre- and/or postnatal toxicity following exposure to iprovalicarb and therefore, no additional safety factors are necessary to protect the safety of infants and children.

## II. EXPOSURE ASSESSMENT

1. Dietary (Food) Exposure Considerations
(*Correspondence:* W. Cutchin to C. Christensen dated March 6, 2002)

The action for iprovalicarb reviewed at this time is an import-only tolerance on grapes, there are no domestic registrations. There are five foliar applications at 0.12-0.48 kg ai/ha (0.11-0.43 lb ai/A) allowed. There are currently no Mexican, Canadian, or Codex MRLs for iprovalicarb. Since the only crop for which a tolerance is requested has no animal feed items of regulatory interest, transfer of residues to meat and/or milk is unlikely.

Iprovalicarb, parent-only, is the residue of interest. Iprovalicarb is not translated into the plant. Residues are primarily found on the surface. Once internalized, the metabolism proceeds via hydroxylation of the 4-methyl group to 4-hydroxymethyl iprovalicarb, which is subsequently conjugated with glucose. The data indicated that iprovalicarb residues do not concentrate in grape juice, must, or wine, but concentrates slightly in raisins. The average concentration/reduction factors were 0.65x for must and wine, 0.27x for juice, and 1.23x for raisins. Decline studies indicate that iprovalicarb residues in/on grapes decrease with time.

The residue database for grapes is from residue field trials only. The reported method LOQ is 0.05 ppm for plant commodities. Residues of iprovalicarb were 0.11-1.5 ppm in/on 44 samples of grapes harvested 28 days. Percent of crop treated data are not available. The chronic dietary (food only) analysis was a Tier 1.

2. Dietary (Drinking Water) Exposure Considerations

This action is for the establishing the import tolerance for improvalicarb on grapes and raisins. Therefore, no domestic drinking water exposures to this chemical are anticipated.

3. Residential Exposure Considerations

This action is for the establishing the import tolerance for improvalicarb on grapes and raisins. Therefore, no domestic residential exposures to this chemical are anticipated.

## III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

1. FQPA Safety Factor Recommendation

The FQPA SFC recommends that OPP depart from the default 10X additional safety factor and instead use a different additional safety factor of 1X. This recommendation is based on reliable data supporting the findings set forth below.

A. Traditional Additional Safety Factor(s) (Addressing Data Deficiencies)

The HIARC concluded that the toxicological database for iprovalicarb is complete and adequate for FQPA assessment; a developmental neurotoxicity study was not required for this chemical and no additional safety factors are needed to account for toxicology data deficiencies.

B. Special FQPA Safety Factor(s)

The FQPA SFC recommends that no Special FQPA Safety Factor is necessary to protect the safety of infants and children in assessing iprovalicarb exposure and risks.

2. Rationale and Findings Regarding Recommendation on Special FQPA Safety Factor(s)

The Committee concluded that no Special FQPA safety factor is needed because: there is no quantitative or qualitative evidence of increased susceptibility of fetuses in the pre-natal exposure in the rat or rabbit developmental toxicity study; although there is qualitative evidence of susceptibility in the multi-generation reproduction study in the rat, it was concluded that there is a low degree of concern (and no residual uncertainty) for the effects seen (Refer to Section I. 3); the HIARC concluded that a developmental neurotoxicity study is not required, and there are no data deficiencies or residual uncertainties identified in the hazard or dietary food exposure data bases for this import-

tolerance only registration of iprovalicarb (no drinking water or residential exposures are anticipated).

3. Application of the Special FQPA Safety Factor (Population Subgroups / Risk Assessment Scenarios)

The FQPA SFC recommends that no Special FQPA Safety Factor is necessary to protect the safety of infants and children in assessing iprovalicarb exposure and risks. This recommendation is applicable to all population subgroups for all exposure routes and durations.



5

4. Summary of FQPA Safety Factors

| Summary of FQPA Safety Factors for Iprovalicarb | | | | |
|---|---|---|---|---|
| | **LOAEL to NOAEL ($UF_L$)** | **Subchronic to Chronic ($UF_S$)** | **Incomplete Database ($UF_{DB}$)** | **Special FQPA Safety Factor (Hazard and Exposure)** |
| **Magnitude of Factor** | 1x | 1x | 1x | 1x |
| **Rationale for the Factor** | No LOAEL to NOAEL extrapolations performed | No subchronic to chronic extrapolations performed | Toxicity database is complete | No residual concerns regarding pre- or post-natal toxicity or completeness of the toxicity or exposure database |
| **Endpoints to which the Factor is Applied** | Not Applicable | Not Applicable | Not Applicable | Not Applicable |

# FQPA SAFETY FACTOR COMMITTEE MEETING

**March 11, 2002**

**IPROVALICARB**

| Name | Division/Branch |
|---|---|
| Ed Zager | HED |
| W. Dykstra | HED |
| Carol Christensen | HED |
| Jess Rowland | HED |
| Jean Holmes | EFED |
| Dennis Edwards | AD |
| Kathy Davis | BEAD |
| Richard Dumas | SRRD |
| Roz Nelson | HED |
| Susan Morris | HED/TOX |
| Debbie McCall | RD |
| Donna Davis | HED |
| Edwin Budd | HED |
| Bill Cutchin | HED |
| ALAN C. LEVY | HED |
| | |
| | |
| | |
| | |

7