HFA-305

FINDING OF NO SIGNIFICANT IMPACT

FOR

USES OF ROXARSONE IN CHICKENS, TURKEYS, AND SWINE

Salsbury Laboratories (Charles City, Iowa) has filed four Environmental Impact Analysis Reports (EIARs) (attached) for the manufacture and use of their roxarsone products covered under four separate new animal drug applications (NADAs, 7-891, 93-025, 5-414, and 8-274). The Bureau of Veterinary Medicine (BVM) has reviewed these EIARs and finds them inadequate to meet the environmental requirements under 21 CFR 25.1(j), but that they do contain sufficient information on manufacturing (when combined with publicly available information) to grant Salsbury Laboratories' request for conditional exemptions under 21 CFR 25.1(f) from the need to prepare EIARs.

The products manufactured under these four NADAs all contain roxarsone (3-nitro-4-hydroxy-phenylarsonic acid) but, as listed below, the NADAs are for various species, claims and/or formulations and dosages.

NADA 7-891, 3-Nitro® Premixes

Roxarsone premixes (3-Nitro®-10, 3-Nitro® Pig-Pak, 3-Nitro®-20, 3-Nitro®-50, and 3-Nitro®-80) to be mixed with complete feeds at: 25-50 ppm of roxarsone in the feed of growing chickens and growing turkeys for increased rate of weight gain, improved feed efficiency, and improved pigmentation; 25-37.5 ppm in the feed of growing-finishing swine for increased rate of weight gain and improved feed efficiency; 200 ppm in the feed of pigs as an aid in the treatment of swine dysentery (hemorrhagic enteritis or bloody scours).

NADA 93-025, 3-Nitro®-W

Roxarsone soluble powder to be dissolved in drinking water to yield: 20 ppm of roxarsone for use in growing chickens and growing turkeys for increased rate of weight gain, improved feed efficiency, and improved pigmentation; 100 ppm of roxarsone for use in swine as an aid in the treatment of swine dysentery (hemorrhagic enteritis or bloody scours).

NADA 5-414, Ren-O-Sal® Tablets

Roxarsone tablets to be dissolved in drinking water to yield: 20 ppm of roxarsone for use in growing chickens and growing turkeys for increased rate of weight gain, improved feed efficiency, and improved pigmentation; 80 ppm of roxarsone as an aid in preventing coccidiosis due to Eimeria tenella in chicken flocks during the growing period.

NADA 8-274, Pig-Scour Tablets

Roxarsone tablets dissolved in drinking water to yield 100 ppm of roxarsone for use in swine as an aid in the treatment of swine dysentery (hemorrhagic enteritis or bloody scours).

The original approvals of roxarsone for these uses date from the 1940's and early 1950's. The National Academy of Sciences/National Research Council (NAS/NRC) reviewed and evaluated the safety and effectiveness of these previously approved uses of roxarsone and in 1970 published their evaluation in the FEDERAL REGISTER (Sept. 10, 1970, 35 FR 14273). The NAS/NRC review found that additional efficacy data, revised labeling, and updated manufacturing and controls information were needed. Salsbury Labs has provided such information and the actions being taken by BVM on these four NADAs reflects the recommendations made by the NAS/NRC for roxarsone.

The conditional exemption claimed by Salsbury Labs for NADA 7-891 is under 21 CFR 25.1(f)(2)(i)(c) which applies to an animal drug for administration in animal feed to be distributed under conditions of a previously approved animal drug. The conditional exemption claimed by Salsbury Labs for NADAs 93-025, 5-414, and 8-274 is under 21 CFR 25.1 (f)(2)(ii), which applies to an animal drug for administration other than in animal feed to be distributed under conditions of approval of a previously approved animal drug. Roxarsone is a previously approved animal drug, has already been marketed for these uses for decades, and the requested action results in no additional indications, increased drug dose or duration of dosing. If no action were taken on these applications, the drug would continue to be marketed for these uses. Approval of the NADAs should result in no increased introductions of roxarsone into the environment and, therefore the conditional exemptions requested apply.

The Bureau of Veterinary Medicine has carefully considered the potential environmental impact of these actions and has concluded that they will not have a significant effect on the human environment and that an environmental impact statement therefore will not be prepared.

In making a determination of no significant impact, the Bureau is aware that roxarsone is an arsenic-containing product and that in the past there has been concern regarding the release of pollutants due to the manufacture of roxarsone by Salsbury Labs (EPA, 1978 and 1979). This was investigated by the EPA and in 1979 corrective actions regarding treatment and disposal of wastes were required of Salsbury Labs. Salsbury Labs states in their EIARs that they now comply with all applicable emission requirements (see below).

1. Under 21 CFR 25.1(g), whenever an applicant requests a conditional exemption under 25.1(f)(1) through (3), the applicant must furnish "an analysis of the environmental effects of the manufacturing process of the article that is the subject of the requested action, which shall include:

(i) An identification of the pollutants expected to be emitted;

(ii) A citation of applicable Federal, State, and local emission requirements; and

(iii) A certification that such emission will comply with said requirements."

Salsbury Labs has partially satisfied these requirements by submitting an EIAR for each of their roxarsone NADAs. While the EIARs certify that Salsbury Labs emissions will comply with all applicable standards, the EIARs submitted do not specifically identify the pollutants emitted or cite any emission requirements.

Salsbury Labs claims that such specific emission data and information "are protected from disclosure by 18 U.S.C. 1905 or 21 U.S.C. 331(j) and need not be included in environmental documents prepared under 21 CFR Part 25." Specific lists of emissions were consequently included in the NADAs but not the EIARs. The types and amounts of pollutants emitted due to the manufacture of roxarsone (and other arsenicals) by Salsbury Labs up to 1978 are already listed in a publicly available document (EPA, 1978). This document does not reflect any corrective action subsequently implemented by Salsbury Labs. It should be understood that this document is not limited to the pollutants emitted (at that time) due solely to the manufacture of roxarsone and that this document probably does not accurately reflect the types and quantities of pollutants presently being emitted by Salsbury Labs. Nevertheless, some of the key tables from the EPA document (1978) are appended to this Finding of No Significant Impact (FONSI) to represent a worst case possibility for emissions from Salsbury Labs (see Appendix A).

In the submitted EIARs, Salsbury Labs has cited the Federal, State and local agencies responsible for monitoring air, wastewater, and landfill standards and, where appropriate, permit numbers. However, specific applicable emission requirements were not listed. Therefore, as supplemental information, following is our listing of Federal standards and/or criteria for arsenic -

a. Occupational - OSHA (1978) limits occupational exposure to inorganic arsenic to 10 $\mu g/m^3$ of air, based on an 8 hour time-weighted average.

b. Hazardous Wastes - The EPA (1981) identifies the following as hazardous wastes -

   i) Wastewater treatment sludges generated during the production of veterinary pharmaceuticals from arsenic or organo-arsenic compounds (EPA Hazardous Waste No. K084).

ii) Distillation tar residues from the distillation of aniline compounds in the production of veterinary pharmaceuticals from arsenic or organo-arsenic compounds (EPA Hazardous Waste No. K101).

iii) Residue from the use of activated carbon for decolorization in the production of veterinary pharmaceuticals from arsenic or organo-arsenic compounds (EPA Hazardous Waste No. K102).

c. Water Quality - The EPA (1980) criteria for arsenic are -

i) For freshwater aquatic life the concentration of total recoverable trivalent inorganic arsenic should not exceed 440 µg/l at any time.

ii) For saltwater aquatic life acute toxicity occurs at concentrations as low as 508 µg/l.

iii) For human health the ambient water concentrations should be zero but that appears unattainable at the present time. Therefore, the levels which may result in an incremental increase of cancer risk over a lifetime are estimated at one per hundred thousand, one per million, or one per ten million. The corresponding recommended criteria are 22 ng/l, 2.2 ng/l, and 0.22 ng/l, respectively.

2. There are several recent references pertinent to the standards for and measurements of the environmental introduction, fate, and effects of arsenic compounds. Following is a brief listing of pertinent recent references.

Axelson, O., Dahlgren, E. Jansson, C.D., and Rehnlund, S.O. 1978. Arsenic exposure and mortality: A case-referent study from a Swedish copper smelter. Br. J. Indust. Med. 35:8-15.

EPA. 1978. NPDES Compliance Monitoring and Water/Waste Characterization. Salsbury Laboratories/Charles City, Iowa (June 19-30, 1978). US-EPA, Office of Enforcement, National Enforcement Investigation Center-Denver and Region VII-Kansas City. EPA-330/2-78-019. 166 pp.

EPA. 1979. Status Assessment of Toxic Chemicals - Arsenic. US-EPA, Office of Research and Development, Cincinnati, OH. EPA-600/2-79-210b. 36 pp.

EPA. 1980. Ambient Water Quality Criteria for Arsenic. US-EPA, Office of Water Regulations and Standards, Washington, D.C. EPA 440/5-80-021. 211 pp.

EPA. 1981. Identification and listing of hazardous waste; final rule and temporary suspension of interim final rule. Federal Register 46(11):4614-4620 (Jan. 16).

Feinman, S.F. and J.C. Matheson, III. 1978. Organic arsenicals, pp. A-117 to A-130 in DEIS: Subtherapeutic Antibacterial Agents in Animal Feeds. U.S. Food and Drug Administration. Rockville, MD.

Fowler, B.A. 1977. Toxicology of environmental arsenic, pp. 79-122 in Toxicology of Trace Elements, Advances in Modern Toxicology, Vol. 2. R.A. Goyer and M.A. Mehlman, eds., Hemisphere Pub. Corp., Washington, D.C.

Fowler, B.A. et al. 1979. Arsenic, pp. 19-33 in A Review of the EPA Red Book: Quality Criteria for Water. R.V. Thurston, R.C. Russo, G.M. Fetterolf, T.A. Edsall, and Y.M. Barber, eds. Water Quality Section, American Fisheries Soc., Bethesda, MD.

NAS. 1977. Arsenic. National Academy of Sciences, Washington, D.C. 332 pp.

NIEHS. 1977. Proceedings of the International Conference on Environmental Arsenic. Published as 41 articles in Environmental Health Perspect. 19:1-242.

OSHA. 1978. Occupational exposure to inorganic arsenic, final standard. Federal Register 43(88):19584-19630) (May 5).

Pinto, S.S., Henderson, V. and Enterline, P.E. 1978. Mortality experience of arsenic-exposed workers. Arch. Environ. Health 33:325-330.

Webb, K.E. and J.P. Fontenot. 1975. Medicinal drug residues in broiler litter and tissues from cattle fed litter. J. Animal Sci. 41:1212-1217.

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Attachments