Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No. 1272/2008 (CLP Regulation)

Pethoxamid

(CAS No. 106700-29-2)

(Index No. 616-145-00-3)

Comments Submitted by the FMC Corporation

(FMC Document No. 70022)

June 9, 2022

Proposed classification based on CLP criteria:

Current CLH in Annex VI	Acute Tox, Cat. 4* Skin Sens., Cat. 1 Aquatic Acute 1 (M=100) Aquatic Chronic 1	H302 H317 H400 H410
Dossier submitter's (DS) proposal	Acute Tox, Cat. 4 (oral: ATE = 983 mg/kg bw) Skin Sens. Cat. 1A Aquatic Acute 1 (M=100) Aquatic Chronic 1 (M=10)	H302 H317 H400 H410
Applicant's (FMC) proposal	Acute Tox, Cat. 4 (oral: ATE = 983 mg/kg bw) Skin Sens. Cat. 1A Aquatic Acute 1 (M=100) Aquatic Chronic 1 (M=10)	H302 H317 H400 H410

Executive Summary

FMC submits the following comments for consideration by the Risk Assessment Committee (RAC) regarding the proposed Harmonised Classification and Labelling of pethoxamid.

FMC agrees with the Dossier Submitter (DS) that it is appropriate to classify pethoxamid for Acute Tox, Cat. 4 (ATE = 983 mg/kg bw) (H302), Skin Sens., Cat. 1A (H317), Aquatic Acute 1 (M-factor = 100) (H400), and Aquatic Chronic 1 (M-factor = 10) (H410).

FMC agrees with the DS that pethoxamid does not meet the classification criteria for genotoxicity, carcinogenicity, reproductive toxicity, specific target organ toxicity – single and repeated exposure, and aspiration hazard.

Introduction

The DS has proposed harmonised classification and labelling for pethoxamid in accordance with the CLP criteria. FMC submits the following comments in response to this proposal during the commenting period.

Physicochemical Properties and Physical Hazards

FMC agrees based on the physical and chemical properties of pethoxamid that classification for physiochemical properties and physical hazards it not required.

Evaluation of Health Hazards

Acute toxicity

Based on the available data, the lowest acute oral LD50 (ATE) was 983 mg/kg bw for male rats exposed to pethoxamid. Thus, FMC agrees with the proposal that pethoxamid be classified for acute oral toxicity (Acute Tox Category 4, H302).

FMC agrees no classification is warranted for acute dermal and inhalation toxicity. FMC also concurs that pethoxamid is not a skin or eye irritant and that classification is not required.

Skin sensitization

Based on the available data from the guinea pig maximization test (GPMT), an intradermal induction at a concentration of 0.5% (v/v) in Alembicol D, followed by a topical challenge at 25 & 12.5% (v/v) in Alembicol D, resulted in 95% of animals producing a positive response to pethoxamid. An intradermal induction concentration (v/v) of >0.1% - ≤1.0% and a challenge sensitization response of ≥60% is considered strong potency and results in a predicted subcategorization of '1A' for skin sensitization. Thus, FMC agrees with the proposal that pethoxamid be classified for skin sensitization (Skin Sensitizer Category 1A, H317).

Germ cell mutagenicity

Based on results of a battery of *in vitro* and *in vivo* genotoxicity studies, it can be concluded that pethoxamid is unlikely to be genotoxic and thus does not meet the classification criteria for germ cell mutagenicity.

Carcinogenicity

FMC agrees with the DS's proposal to not classify pethoxamid for carcinogenicity, based on the lack of human relevance of liver tumours observed in mice and thyroid tumours observed in rats following treatment with pethoxamid.

Recent additional mechanistic of action (MOA) data has been generated that includes a side-by-side assessment of phenobarbital, a model rodent liver and thyroid tumour inducer, to ensure a direct comparison to pethoxamid. These data strongly demonstrate that the hepatocellular adenomas/carcinomas and thyroid follicular cell adenomas observed in rodents treated with high doses of pethoxamid are not relevant to humans.

Pethoxamid has been demonstrated to be a weak inducer of CAR (Constitutive Androstane Receptor) in mouse hepatocyte cultures; and in an *in vitro* species comparison assay, pethoxamid induced cell proliferation in mouse hepatocytes but not in human hepatocytes. The available data with pethoxamid supports the following MOA where the molecular initiating event is activation of CAR followed by increased cell proliferation leading to increased preneoplastic foci and ultimately increased hepatocellular adenomas. Based on the difference in biological response in humans and rodents to CAR activation, any hepatocellular adenomas developed in mice through activation of these nuclear receptors by pethoxamid in mice, are not of relevance to humans. Therefore, it can be concluded that pethoxamid does not pose a hepatic carcinogenic hazard to humans.

Based on a recent thyroid MOA study with pethoxamid in rats, it can be concluded that liver enzyme induction, leading to increased hepatic T4 glucuronidation and clearance, elicited a feedback response on the thyroid via an increase in TSH, resulting in associated thyroid follicular cell hypertrophy and hyperplasia due to functional compensation by the thyroid. The results with pethoxamid were consistent with those of phenobarbital, which was included in the study. In a separate biliary excretion study, increased clearance of T4-glucuronide by the liver was demonstrated in pethoxamid-treated rats, consistent with that of phenobarbital, which was included in the study. As noted in the ECHA Guidance on the Application of the CLP Criteria (July 2017), some rodent tumours are not considered relevant for humans, including thyroid tumours mediated by UDP glucuronyltransferase induction. Thus, a concordant and highly plausible MOA has been established for pethoxamid-induced thyroid follicular cell adenomas in rats, a MOA that is not relevant to humans. Therefore, it can be concluded that pethoxamid does not pose a thyroid carcinogenic hazard to humans.

Thus, FMC agrees that pethoxamid does not meet the classification criteria for carcinogenicity (conclusive but not sufficient for classification).

Reproductive Toxicity

The reproductive toxicity of pethoxamid was investigated in a rat two-generation reproduction study and in developmental toxicity studies in rats and rabbits. FMC agrees that pethoxamid does not meet the classification criteria for reproductive or developmental toxicity, since pethoxamid did not cause adverse effects on sexual function and fertility or produce evidence of developmental toxicity. FMC also agrees that pethoxamid does not meet the classification criteria for adverse effects on or via lactation.

Specific Target Organ Toxicity – Single Exposure

FMC agrees that pethoxamid does not meet the classification criteria for Specific Target Organ Toxicity – Single Exposure. No single organ effect was observed in males and females exposed to a single oral (gavage) dose of pethoxamid. Furthermore, functional observation battery results indicate that pethoxamid does not cause acute neurotoxicity.

Specific Target Organ Toxicity – Repeat Exposure

FMC agrees that pethoxamid does not meet the classification criteria for Specific Target Organ Toxicity – Repeat Exposure. Findings in rat, mouse, & dog studies reflected general non-specific effects, adaptive changes, or of insufficient magnitude or severity to be indicative of STOT-RE and thus no classification is appropriate.

Aspiration Hazard

FMC agrees that pethoxamid is a solid and thus does not pose an aspiration hazard.

Evaluation of Environmental Hazards

FMC agrees that pethoxamid meets the classification criteria for both acute and chronic aquatic ecotoxicity (Aquatic Acute 1, M-factor = 100 [H400] and Aquatic Chronic 1, M-factor = 10 [H410]).