SUBSTANCE EVALUATION

CONCLUSION DOCUMENT

as required by REACH Article 48

for

Tributyl phosphate

EC No 204-800-2

CAS No 126-73-8

Evaluating Member State(s): Hungary

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Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2012

Member State concluded the evaluation without the need to ask further information from the registrants under Article 46(1) decision.

Please find (search for) further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work.

In order to ensure a harmonised approach, ECHA in cooperation with the Member States developed risk-based criteria for prioritising substances for substance evaluation. The list of substances subject to evaluation, the Community rolling action plan (CoRAP), is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by the Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. In this conclusion document, the evaluating Member State shall consider how the information on the substance can be used for the purposes of identification of substances of very high concern (SVHC), restriction and/or classification and labelling. With this Conclusion document the substance evaluation process is finished and the Commission, the registrants of the substance and the competent authorities of the other Member States are informed of the considerations of the evaluating Member State. Thus this conclusion document is not reflecting an official position of ECHA. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

CONTENTS

1. CONCERN(S) SUBJECT TO EVALUATION

Tributyl phosphate was originally selected for substance evaluation in order to clarify suspected risks about:

- *Carcinogenicity and mutagenicity:* Based upon several studies epithelial hyperplasia of the urinary bladder was evident and urinary bladder papillomas or carcinomas also appeared. As all the mutagenicity tests were negative, tributyl phosphate may be considered a non-genotoxic carcinogenic substance. However, in relation to the carcinogenicity, the re-assessment of potential genotoxic potential of tributyl phosphate might be useful.

- *Specific Target Organ Toxicity:* The repeated dose studies suggest that the primary target organs of toxicity of tributyl phosphate are the liver and the urinary bladder. Absolute and relative liver weight elevation, hepatocyte hypertrophy, changes of clinical chemistry parameters and hepatocellular adenomas could be observed. Further to this, some studies suggest that tributyl phosphate might have adverse effects on kidney, spleen and testes as well.

- *Neurotoxicity:* Data available in the literature on the neurotoxic potential of tributyl phosphate seem to be contradictory. The studies submitted in the registration dossiers indicate no neurotoxic effects. However there are studies in which cholinesterase inhibition, cholinergic effects and other neurotoxic symptoms were described.

- *Developmental toxicity:* Tributyl phosphate might have teratogenic properties as long-term treatments resulted in decreased pup weights and delayed ossification coupled with underdeveloped, rudimentary ribs in rabbits.

During the evaluation no further concerns to be clarified under substance evaluation process were identified.

2. CONCLUSION OF SUBSTANCE EVALUATION

The available information on the substance and the evaluation conducted has led the evaluating Member State to the following conclusions, as summarised in the table below.

Conclusions	**Tick box**
Need for follow up regulatory action at EU level	
Need for Harmonised classification and labelling	
Need for Identification as SVHC (authorisation)	
Need for Restrictions	
Need for other Community-wide measures	
No need for regulatory follow-up action	X

3. JUSTIFICATION FOR THE CONCLUSION ON THE NEED OF REGULATORY RISK MANAGEMENT

3.1. NEED FOR FOLLOW UP REGULATORY ACTION AT EU LEVEL

3.1.1. Need for harmonised classification and labelling

No need for harmonised classification and labelling.

3.1.2. Need for Identification as a substance of very high concern, SVHC (first step towards authorisation)

No need for identification as a substance of very high concern, SVHC.

3.1.3. Need for restrictions

No need for restriction.

3.1.4. Proposal for other Community-wide regulatory risk management measures

No need for other Community-wide regulatory risk management measures.

3.2. NO FOLLOW-UP ACTION NEEDED

The concern could be removed because	**Tick box**
Hazard and /or exposure was verified to be not relevant and/or	*X*
Hazard and /or exposure was verified to be under appropriate control and/or	
The registrant modified the applied risk management measures.	
other:	

Based upon the detailed evaluation of available information (aggregated registration dossier, Chemical Safety Report, other scientific evidence described in studies and literature), the evaluating Member State was in the position to clarify all the above listed concerns. It could be established that none of the above listed concerns are warranted. The available information is sufficient and reliable to conclude on these concerns, and there is no need of further studies or other information on these end-points. Further to this, no new concern was raised during the current substance evaluation.

Consequently, there is no need to take any additional risk management measures concerning the evaluated end-points, and the current CLP classification of the substance is appropriate.

The concerns originally raised and listed above may be rejected due to the following reasons.

Carcinogenicity and mutagenicity

There were three available studies in rodents (mice and rats) which are considered reliable (Klimish reliability factor 1), but also sufficient to evaluate carcinogenicity. In two studies only pro-carcinogenic alterations (i.e. transitional cell carcinoma) were observed by the highest dose (3000 ppm) dietary intake in rats, in the urinary bladder of both sexes. Other alterations as bladder hyperplasia and papillomas in the urinary bladder were also found in female rats only at a lower concentration (700 ppm). Similar changes were not found in the same rat strain in an earlier reliable study. No suspicions referring to human carcinogenicity have ever been published. Since no similar effects have been found in mice, these effects might be species specific to rats.

Based on the available and reliable experimental data the concerns on possible more serious carcinogenic properties of tributyl phosphate can be rejected.

The genotoxic properties of the substance were also examined by the evaluating Member State and the reasoned opinion shows that no mutagenic activity of it can be demonstrated. All acceptable tests (bacterial mutagenicity, in vitro gene mutation, in vivo cytogenicity) gave negative results.

Specific Target Organ Toxicity

The evaluating Member State has examined the possible adverse effects of tributyl phosphate in urinary bladder, liver, kidney, spleen and testes; although in the toxicokinetic studies it was revealed that the major excretory route for the radio label of tributyl phosphate was the urine.

Based on the observed effects in the experiments described in relevant literature the following conclusions were drawn.

Urinary bladder

In case of urinary bladder alterations observed in the short term repeated dose toxicological studies, namely different epithelial hyperplasias, postulate the non-genotoxic mode of action that can lead to neoplastic lesions observed in longer term toxicological studies. Numerous agents have been identified that produce superficial or deep cytotoxicity and regeneration, and are associated with increased incidences of bladder tumors in rodents. Similar toxic and regenerative processes appear to be involved with bladder carcinogenesis in humans related to chronic inflammation, such as schistosomiasis and calculi. Based on the findings it can be concluded that the effect observed in urinary bladder is due to a target organ toxicity of tributyl phosphate.

The purpose of STOT RE is to identify the primary target organ(s) of toxicity (CLP Annex I, 3.9.1.4) for inclusion in the hazard statement. As it is stated in the Guidance on application of CLP criteria, STOT RE should only be assigned where the observed toxicity is not covered more appropriately by another hazard class. The observed changes in urinary bladder following repeated exposure to tributyl phosphate can be considered as covered appropriately by the Carcinogenic category 2 classification (CLP).

Liver

Animal studies have shown no significant accumulation of tributyl phosphate in the liver. Results from most of the repeated dose studies consistently showed increased liver weight of rats and mice, but it should be noted, that the dose was in all of these studies high. Some of these studies described elevated liver enzymes activity, a part of these enzymes are connected to the metabolism of the tributyl phosphate. The studies provide adequate basis for evaluating the repeated dose toxicity. The findings indicate that tributyl phosphate is not hepatotoxic.

Kidney, spleen and testes

As the main excretory route for the radio label of tributyl phosphate is the urine, the role of the excreted substance or metabolites in the development of kidney changes cannot be excluded. However, the effective dose of kidney alterations in various relevant studies is well above the guidance value described in Guidance on the Application of the CLP Criteria.

Spleen alterations, namely the changes of the organ weight were observed in two studies at dose levels above the guidance values.

No effects on testes were observed either in the conclusive majority of longer term repeated dose studies or in 2-generation reproduction study. In addition no effect on male fertility was observed in the reproduction toxicity study.

Considering the evidences overviewed above, the concerns on the possible target organ toxicity for kidneys, spleen and testes are not warranted.

Neurotoxicity

The generally recommended strategy for neurotoxicity testing (Costa, 1998; OECD, 2004) was followed in the relevant studies. The observed symptoms were non-specific, consequently no further specific tests of motor and sensory functions were carried out. Therefore, only few publications exist about additional specific investigation of tributyl phosphate. Nevertheless, neurotoxicity of tributyl phosphate has been tested in all relevant fields: neurobehavioral, neuropathological, neurophysiological and neurochemical techniques were all applied to complete the knowledge about tributyl phosphate.

Based on the available scientific publications it can also be concluded that cholinesterase inhibition by tributyl phosphate is weak. Substantial cholinesterase inhibition in exposed animals was reported in one study only from rats that received a lethal dose of tributyl phosphate, however, this study was deemed unreliable in several available evaluations.

The conclusions of short-term and long-term, single dose and repeated dose toxicity studies were that nervous system is not target organ of tributyl phosphate. If neurotoxic effects were detected in some studies they appeared only after exposure to very high doses, they were unspecific, transient, probably caused indirectly by other organ damages and/or general toxicity of tributyl phosphate.

Developmental toxicity

The teratogenicity studies for the developmental toxicity of tributyl phosphate were performed in two species (two strains of rats and one strain of rabbits). The studies involved range-finding experiments. Embryotoxic and foetotoxic effects, such as ossification disturbances (delayed ossification and rudimentary ribs) occurred only at

maternally toxic doses. The studies were reliable and sufficient to conclude that teratogenic effect of tributyl phosphate could not be substantiated, therefore it can be stated that the hazard concern regarding teratogenicity of tributyl phosphate is not justified.

Further to the above, no specific adverse effects of tributyl phosphate on the reproduction were reported in the literature as yet. Any effects noted were sporadic and without any clear correlation with the treatment. Consequently, the available data do not suggest any specific, selective effects of tributyl phosphate on reproductive parameters or fertility. Reproductive organs were not identified as target organs of tributyl phosphate in the available studies.

4. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

No follow-up action is deemed necessary by the evaluating Member State.