EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-0000003321-87-03/F Helsinki,9 October 2013

DECISION ON A COMPLIANCE CHECK OF A REGISTRATION PURSUANT TO ARTICLE 41(3) OF REGULATION (EC) NO 1907/2006

For Sodium Bromide, CAS No 7647-15-6 (EC No 231-599-9), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration dossier for Sodium Bromide, CAS No 7647-15-6 (EC No 231-599-9), submitted by [redacted] (Registrant), latest submission number [redacted], for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates after 01 August 2013, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

This compliance check decision does not prevent ECHA from initiating further compliance checks on the present dossier at a later stage.

The compliance check was initiated on 21 November 2012.

On 16 April 2013 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision. That draft decision was based on submission number [redacted].

By 17 May 2013 the Registrant did not provide any comments on the draft decision to ECHA.

On 1 August 2013 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals to amend the draft decision within 30 days of the receipt of the notification.

Subsequently, Competent Authorities of the Member States did not propose amendments to the draft decision and ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Information required

1) Pursuant to Articles 41(1)(a), 41(3) and 10(a)(ii) as well as Annex VI , section 2 of the REACH Regulation the Registrant shall submit for the registered substance:

Analytical data for quantification of the sodium ion and a description of the method (or the appropriate bibliographical references) used for the quantification (Annex VI, 2.3.7).

2) Pursuant to Articles 41(1)(a), 41(3), 3(28), 10(a)(vii), 12(1)(e) and 111, as well as Annex X and Annex I section 1.1.4. of the REACH Regulation the Registrant shall submit robust study summaries in the IUCLID format for the following information:

   a. Repeated dose toxicity (Annex VIII and IX, 8.6.1 and 8.6.2), as specified in section III.2)a. below;
   b. Two-generation reproductive toxicity study (Annex X, 8.7.3.), as specified in section III.2)b. below;
   c. Pre-natal developmental toxicity study (Annex IX and X, 8.7.2.), as specified in section III.2)c. below;
   d. Effects on endocrine parameters (Annex I, 1.1.4,) as specified in section III.2)d. below;

3) Pursuant to Articles 41(1)(a), 41(3), 3(29), 10(a)(vi), 12(1)(e), and Annex XI, 1.1.3. of the REACH Regulation the Registrant shall submit study summaries for the following information:

   a. Human data as specified in section III.3)a. below;

4) Pursuant to Articles 41(1)(c), 10(b), 14 and Annex I, section 1 of the REACH Regulation the Registrant shall submit in the chemical safety report:

   a. Justification for the selection of the studies used to establish the Derived no effect levels (DNELs) (Annex I, 1.1.4), as specified in section III.4)a. below;

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated IUCLID dossier to ECHA by **9 April 2014.**

III. Statement of reasons

Based on the examination of the technical dossier, ECHA concludes that the information therein, submitted by the Registrant for registration of the above mentioned substance for the purpose of registration within the applicable tonnage band of 1000 tonnes or more per year in accordance with Article 6 and 11(2) of the REACH Regulation, does not comply with the requirements of Articles 3(28), 3(29), 10 and 12 or with Annexes I, VI, X and XI thereof. Consequently, the Registrant is requested to submit the information mentioned above that is needed to bring the registration into compliance with the relevant information requirements.

1) Missing information related to substance identity

Pursuant to Article 10(a)(ii) and Annex VI, section 2 of the REACH Regulation, the technical dossier of the registration shall include information on the identity of the substance. Annex VI, section 2 lists information requirements that shall be sufficient to identify the registered substance.

The registration did not contain details of the analytical method(s) or a description of the method(s) (or the appropriate bibliographical references) used for the quantification of the sodium ion which is required by Annex VI, section 2.3.7. of the REACH Regulation.

The Registrant is hereby required to submit the missing information.

2) Missing information related to robust study summaries

Pursuant to Articles 10(a)(vii) and 12(1)(e) of the REACH Regulation, a registration for a substance produced in quantities of 1000 tonnes or more per year shall contain robust study summaries of the information derived from the application of Annexes VII to XI if required under Annex I. Pursuant to Articles 10(a)(vii) and 111, the technical dossier containing robust study summaries shall be provided in the IUCLID format.

Annex I section 1.1.4 provides that "*If there are several studies addressing the same effect, then, having taken into account possible variables (e.g. conduct, adequacy, relevance of test species, quality of results, etc.), normally the study or studies giving rise to the highest concern shall be used to establish the DNELs and a robust study summary shall be prepared for that study or studies and included as part of the technical dossier. Robust summaries will be required of all key data used in the hazard assessment. If the study or studies giving rise to the highest concern are not used, then this shall be fully justified and included as part of the technical dossier, not only for the study being used but also for all studies demonstrating a higher concern than the study being used. It is important irrespective of whether hazards have been identified or not that the validity of the study be considered.*"

According to Article 3(28) of the REACH Regulation, a robust study summary is a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study minimising the need to consult the full study report. ECHA has described how to report robust study summaries in the Practical Guide 3 (How to report robust study summaries, Version 2.0 – November 2012).

While the issue of missing robust study summaries is discussed in the current section, section 4 focuses on the missing information related to the chemical safety report and the selection of the key data for the establishment of DNEL within the meaning of Annex I, section 1.1.4.

a) Repeated dose toxicity studies

In IUCLID section 7.5.1 the Registrant included a total of 7 endpoint entries for studies on repeated dose toxicity conducted via the oral route. Five of the studies have been conducted in the rat. Two of the studies have been conducted in dogs. These studies in dogs are not further discussed below.

The study selected as a key study with an assigned reliability 1 [redacted] was conducted according to GLP (good laboratory practice) and OECD guidelines, however the test was not carried out with the registered substance. The tested substance was another bromide salt, ammonium bromide. The conclusion by the registrant for this study is: "*Under the conditions of this study, there were clear changes in both sexes at dose levels of 225 mg Ammonium bromide/kg/day or greater, but there was no associated histopathology. At 100 mg/kg/day effects were limited to slight limpness in occasional males.*" The relevant observations in this study are related to neurotoxicity. The NOAEL estimated from this study is 100 mg/kg bodyweight/day with the notion: "*endpoint based on clinical signs in next higher dose level. NOAEL for male animals close to 100 mg/kg bw/day*". As the starting point for the DNEL derivation 95 mg/kg bw/day was chosen, but without justification as to why "*close*" to 100 mg/kg bw/day can be translated into 95 mg/kg bw/day. As justification for using read across the following

was provided: "*Read across from other Bromide salts to NaBr is possible due to the full dissociation of the compound in water. Na+, K+, or NH4+ are not toxic in the concentration range where BR- is toxic. Therefore only the BR- is responsible for the toxicity effects*" (from CSR page 17)..

In the IUCLID dossier there are also studies reported which were conducted in the rat with the registered substance. A 4–week non GLP and non-guideline study in the rat with sodium bromide administration via diet with assigned reliability 2 (Short-term Toxicity Study on Sodium Bromide in Rats, oral.001, 1973). A NOAEL of 4800 ppm in the diet has been determined. A published 90-day non-GLP non-guideline study in the rat with sodium bromide administration via the diet with an assigned reliability 2 is also included in the registration dossier ([redacted]). Information provided in an attached file states that the NOAEL of 300 ppm determined in this study equals 15 mg Br^- ion/kg bw/day. These two studies (oral.001 and oral.002) were not identified as key studies. Another 90-day non-GLP non-guideline study in the rat [redacted] reported the results of sodium bromide in the normal diet in comparison with a chloride reduced diet. The test result is equivalent to: NOAEL = 97 ppm for the bromide ion. The Registrant identified this study as a key study and contradictorily assigned a reliability of 3 in the IUCLID file while assigning the same study a reliability of 2 in an attached file.

In addition, the Registrant has included a long-term study in rats that was conducted with potassium bromide in the diet with only one dose but with an assigned reliability 2 [redacted]. The NOAEL of 500 ppm potassium bromide in the diet determined, according to the entry in IUCLID, is equivalent to: 16.5 mg/kg bw/day (males) and 20.0 mg/kg bw/day (females), or 11.1 mg(Br^-)/kg bw/day (males) and 13.4 mg (Br^-)/kg bw/day (females). This study has been flagged as a key study by the Registrant. From the IUCLID information provided, the study design and the role of potassium bromide in this design is not clear. It appears from the title of the study that the main purpose of the study was to investigate methyl bromide fumigated diet and that a potassium bromide group was used as a sort of control group. It is also not clear what relevance the Registrant attaches to the study conducted with potassium bromide for the dossier for sodium bromide. If the reasoning of the Registrant with regard to possible read across from other bromide salts is applied (see above), the results of the two-year study conducted with potassium bromide contribute significantly to the assessment of sodium bromide and should be described in detail in IUCLID.

ECHA notes that the reported studies conducted with the registered substance in the rat (oral.001, 002, 003) have identified NOAELs considerably lower than the key study conducted with ammonium bromide. Moreover, the Registrant summarises the studies with sodium bromide (the registered substance) in the CSR: "*... sodium bromide caused behavioural changes, growth reduction, increased thyroid and adrenals weights, and a dose-related disturbance of the endocrine system. The NO(A)EL for rats was 15 mg (Br-) /kg bw/day from the 90-day oral study.*" Similarly, it needs to be clarified whether the above study oral.007 conducted with potassium bromide is relevant in this sense. ECHA considers that the choice of the key study contradicts Annex I, 1.1.4 which requires that the study or studies giving rise to the highest concern are used to establish the DNELs and that a robust study summary fulfilling the criteria of Article 3(28) is prepared for that study or studies and included as part of the technical dossier. Furthermore, contrary to Annex I, 1.1.4 the Registrant has not fully justified the use of the study with ammonium bromide as a key study.

ECHA considers that the information currently provided for the studies oral.001, 002, 003 and 007 do not meet the requirements of Article 3(28) of the REACH Regulation governing the content of robust study summaries. More particularly, the IUCLID fields on methods and results contain minimal information. The additional file attached to the IUCLID section contains some more information but it is necessary to provide a detailed report on the methods and the results in the IUCLID fields to allow ECHA to make independent conclusions on the validity of the studies and their use in human health hazard assessment.

The Registrant is therefore requested to provide robust study summaries with the above missing elements for the studies identified as repeated dose toxicity studies oral.001, repeated dose toxicity studies oral.002, repeated dose toxicity studies oral.003 and repeated dose toxicity studies oral.007 in IUCLID section 7.5.1.

b) Two generation reproductive toxicity study

The Registrant included one multi-generation study conducted in the rat with sodium bromide in the diet in IUCLID section 7.8.1 [redacted]. The study is not based on a standard protocol and has been identified as the key study with an assigned reliability of 2. A parental NOAEL of 300 ppm (corresponding to 12 mg Br^-ion /kg bw/day) has been identified. At higher dose levels the fertility of the animals was severely reduced. The NOAEL (pups) has been defined as 1200 ppm (no conversion provided).

ECHA refers to Annex I, section 1.1.4 under which robust summaries will be required for all key data used in the hazard assessment. In this respect, ECHA regards the above study as critical for hazard/risk assessment and classification and labelling. ECHA considers the description of the method and results in the IUCLID file as insufficient to allow an independent evaluation of the results, as required by Article 3(28) of the REACH Regulation. The additional file attached to the IUCLID section contains some more information but a detailed report on the methods and the results in the IUCLID fields is necessary to allow ECHA to make independent conclusions on the validity of the study and its use in human health hazard assessment.

The Registrant is thus required to include a robust study summary with the above missing elements for the multi-generation study (toxicity to reproduction.001) in IUCLID section 7.8.1.

c) Pre-natal developmental toxicity

In IUCLID section 7.8.2 the Registrant included 3 studies on developmental toxicity which are all flagged as key studies. One study was conducted according to GLP and OECD 414 in the [redacted]. A NOAEL (maternal) of 250 mg/kg bw/day and a NOEL (teratogenicity) of 250 mg/kg bw/day were identified (highest dose tested). ECHA, however, observes that the method and the results section are not filled in according to the robust study requirements of Article 3(28) of the REACH Regulation. In particular, it is not specified in the appropriate IUCLID fields what examinations have been conducted and what results have been obtained. Therefore the information provided does not allow ECHA to make an independent assessment of the validity of study and its use in human health hazard assessment.

Another IUCLID entry [redacted] describes the dose range finding study in rabbits

conducted for the aforementioned study 005. Again the study is flagged as a key study with a robust study summary, but the description of the methods used and the results obtained is inadequate. In particular, it is not specified in the appropriate IUCLID fields what examinations have been conducted and what results have been obtained. Therefore it does not allow ECHA to make an independent assessment of the validity of study and its use in human health hazard assessment.

Another study selected as a key study and flagged as having a robust study summary was conducted in rats according to GLP and OECD [redacted]. NOAEL (maternal) and NOEL (teratogenicity) of 100 mg/kg bw/day have been derived. At higher doses adverse effects on the foetuses have been observed (at 300 mg/kg bw/day the LOAEL was identified based on foetal skeletal anomalies and variants), but also lower bodyweight gains in the maternal animals were noted. ECHA points out that contrary to Article 3(28) of the REACH Regulation, the description of the method and results in the IUCLID file does not allow an independent evaluation of the results and in particular it cannot be concluded as to whether the maternal toxicity and the developmental effect are related or not. The additional files attached to the IUCLID sections contain some more information but a detailed report on the methods and the results in the IUCLID fields is necessary to allow ECHA to make independent conclusions on the validity of the study and its use in human health hazard assessment.

ECHA notes that the Registrant has also registered other bromide salts, in particular ammonium bromide (EC number 235-138-8). In fact, an ammonium bromide repeated dose study contained in the ammonium bromide registration dossier is included in the sodium bromide dossier and furthermore this study is used for deriving DNELs for sodium bromide (see section III.2.a) above). However, the Registrant did not include the available ammonium bromide studies on pre-natal developmental toxicity in the sodium bromide dossier, despite his claim that results from studies with other bromide salts can be used to predict effects for the registered substance (see section III.2.a.). This fact highlights the lack of a consistent approach to read across in the dossier according to Annex XI, section 1.5 and Annex I, 0.4. The Registrant did not justify why the studies on repeated dose toxicity conducted with an analogue substance are regarded as key studies and why the prenatal developmental toxicity studies with the same analogue substance are not even mentioned.

The studies cited in the ammonium bromide registration dossier but not contained in the current registration dossier are studies by [redacted] and [redacted]. ECHA notes that in [redacted] relevant developmental effects have been observed at 50 mg/kg body weight in the absence of maternal toxicity. These studies give rise to a higher concern than the results from the above three prenatal developmental toxicity studies with sodium bromide identified as key studies. The results may therefore have a large impact on the assessment of sodium bromide. ECHA regards these studies as potentially very relevant for the assessment of the pre-natal developmental toxicity of sodium bromide and its impact on classification and labelling.

Therefore, the Registrant is requested to include robust study summaries with the above missing elements for the studies identified as key studies in IUCLID section 7.8.2 of the sodium bromide dossier (teratogenicity.001, teratogenicity.002 and teratogenicity.005). In addition, the Registrant is requested to provide robust study summaries of [redacted] as cited in the registration dossier for ammonium bromide and to include these in IUCLID section 7.8.2 of the sodium bromide dossier as additional key studies together with a discussion on their relevance to a possible

classification of sodium bromide.

d) Studies on endocrine parameters

The Registrant has included in IUCLID section 7.9.3 a study on the effects of sodium bromide on endocrine parameters in the rat [redacted]. This study is identified as a key study with a robust study summary.

Indeed, ECHA agrees with the Registrant that this study is essential to understand the mechanism of toxicity. However, contrary to Article 3(28) of the REACH Regulation, the description in the IUCLID file of the methods used and the results achieved does not allow an independent evaluation of the study.

Accordingly, the Registrant shall provide a robust study summary with the above missing elements for the study on endocrine parameters [redacted].

3) Missing information related to study summaries

a) Human data

Article 10(a)(vi) requires the registration dossier to include study summaries of the information derived from the application of Annexes VII to XI.

Annex XI, 1.1.3 of the REACH Regulation sets out the general criteria for describing and assessing the adequacy of human data. The ECHA 'Guidance on information requirements and chemical safety assessment' Appendix R 8-15 provides more details.

According to Article 3(29) of the REACH Regulation, a study summary is a summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make assessment of the relevance of the study. ECHA has described how to report study summaries in the Practical Guide 3 (How to report robust study summaries, Version 2.0 – November 2012).

The Registrant has included in IUCLID section 7.9.3 three studies with human volunteers and has flagged these as key studies with robust study summaries [redacted]. These studies can be regarded as historical human data within the meaning of Annex XI, 1.1.3.

Since these studies investigate the NOEL in humans with a specific emphasis on the endocrine and central nervous system, ECHA regards these studies as potentially relevant in the context of DNEL derivation according to Annex I (1.4). However, contrary to Article 3(29) of the REACH Regulation, the description of the methods used and the results achieved in the IUCLID file does not provide sufficient information to enable assessment of the relevance of the studies. The importance of these studies in the assessment of sodium bromide is emphasised by their use in other international assessment schemes (see below under section 4).

Therefore, the Registrant is requested to provide study summaries with the above missing elements for the human volunteer studies identified as key studies [redacted].

4) Missing information related to the Chemical Safety Report

Annex I sets out the general provisions for assessing substances and preparing chemical safety reports (CSR). Pursuant to Annex I section 0.5 of the REACH Regulation the chemical safety assessment shall be based on the information submitted in the technical dossier and on other available and relevant information. Pursuant to Annex I section 1.1.4. of the REACH Regulation, normally the study or studies giving rise to the highest concern shall be used to establish the DNELs. If the study or studies giving rise to the highest concern are not used then this should be fully justified.

The Registrant has identified a 90-day repeated dose toxicity study with the read across substance ammonium bromide as the key study (see section III.2.a) above) and has used the results of this test as the starting point for long-term DNEL derivation. The justification provided by the Registrant for selecting this test is as follows "*This study was selected as a representative study since this is a recent GLP study, according to OECD guideline 408, using an inorganic salt similar to sodium bromide, with high water solubility. The ion of concern is the bromide ion*".

ECHA considers that, contrary to Annex I section 1.1.4 the Registrant has not sufficiently justified his decision to disregard the studies giving rise to higher concern when establishing the DNELs. In particular those studies presented in the registration dossier which were carried out with the registered substance (studies oral 001, 002 and 003, see section III.2.a) above) report lower NOAELs than that in the chosen key study on ammonium bromide. Also the results of the two-year study with potassium bromide (repeated dose toxicity: oral.007) may need to be considered. Furthermore the critical toxicological endpoint(s) on which the DNEL derivation is based has not been clearly identified. In this context it is also noted that the results of the multi-generation study with sodium bromide (toxicity to reproduction.001) need to be considered, since the parental NOAEL observed in this study appears to be the lowest NOAEL observed in animal studies. In this context is important to note that the fertility of rats has been severely affected by the substance.

Furthermore, although the Registrant regarded ammonium bromide as a relevant analogous substance for read across with regard to repeated dose toxicity he has omitted relevant OECD 414 developmental toxicity studies carried out on ammonium bromide (see section III.2.c) which may give rise to a higher concern than the key studies presented in the registration dossier for developmental toxicity. This study is present in the ammonium bromide joint registration for which the Registrant is the lead registrant.

ECHA further points out that the available experimental human studies (see section III.3.a) have to be considered in arriving at long-term DNELs. Two international assessments for the registered substance (EMEA (1997) *Bromide, sodium salt. Summary report*; FAO/WHO (1989) Bromide ion. In: *Pesticide residues in food—1988 evaluations. Part II—Toxicology*; WHO (2009) *Bromide in drinking-water*) use such human data as key information; however these data were not taken into account by the Registrant in the context of DNEL derivation.

Finally, the substance has been identified by the Registrant as a substance with adverse effects on the endocrine and nervous systems (see section III.2.a above). ECHA points out that the consequences of these properties with regard to long-term DNEL derivations and applied safety factors should be transparently documented. Furthermore a consideration of these properties with regard to sensitive subpopulations (e.g. pregnant women or children) according to Annex I (1.4.1) is currently missing. In the current dossier only overall assessment factors are provided. It is not possible for ECHA to follow the logic of these overall factors and to understand which sub-factors contribute to the overall assessment factor. The tables for DNEL derivation for workers (CSR table 28) for the general population

(CSR table 29) do not identify the critical endpoints, such as endocrine disruption or neurotoxicity, for which the DNELs have been derived. Guidance on DNEL derivation is available in the ECHA 'Guidance on information requirements and chemical safety assessment' (R 8).

Therefore in accordance with Annex I, section 1 of the REACH Regulation, as referred to above, the Registrant is requested to update his CSR and consider all available and relevant non-human and human information when performing hazard assessment and selecting key data for the establishment of DNELs. If the available repeated dose toxicity studies on the registered substance in the derivation of long-term DNELs, including the multi-generation study, giving rise to the highest concern are not used, the Registrant shall provide a full and robust justification for this in line with Annex I, 1.1.4. The results of the developmental toxicity studies on ammonium bromide which may give rise to a higher concern than the key studies selected in the registration dossier should be included in the considerations. Also the human volunteer studies available as well as the clear adverse effects on the endocrine system should be considered in the identification of DNELs. The impact of these considerations on the assessment factors must be documented.

IV. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on ECHA's internet page at http://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

[redacted]
Jukka Malm
Director of Regulatory Affairs