COMMENTS SUBMITTED TO ECHA BY WIBAX AB.

Comments to ECHA regarding the CLH report
"Proposal for Harmonized Classification and Labeling – Substance name Anthraquinone
EC Number 201-549-0
CAS Number: 84-65-1
Version number: 2.0; Date: January 2015

A) General comments

Manufacturing methods and purities of Antraquinone (AQ):

9,10 Anthraquinone (AQ) used today as pulp production additive are manufactured by the methods below:

1. Friedel Crafts Reaction: Synthesis from phthalic anhydride and benzene
2. Diels –Adler reaction: Naphthalene process
3. Vapor-phase oxidation of anthracene with air

<u>1. Phthalic anhydride process (Friedel Craft reaction):</u>
Synthesis of AQ from phthalic anhydride and benzene where aluminum chloride and sulfuric acid is used in the oxidation process [Vogel, 1985]. The purity of the final product is typical 99,2% and the AQ product is free from impurities as aromatic and nitroanthracenes [Butterworth, et al 2001].

<u>2. Diels Adler reaction</u>
Reaction of 1,4 naphtoquinone with 1,3 butadiene followed by oxidation in aqueous solution. [Chung 1978]. Kawasaki Kasei Chemicals use a three step process that begins with oxidation of naphthalene to naphthoquinone, which in turn is reacted with butadiene in a Diels-Adler reaction. The product is then oxidized to AQ in aqueous solution [Vogel 1985]. The resulting product is free from mutagenic impurities [Butterworth et al 2001]

<u>3. Vapor-phase oxidation of anthracene with air</u>
Catalytic oxidation of anthracene with preheated air. After passing through the oxidation reactor the product is lead to the condensation section [Vogel, 1985]. This method is preferred for easy continuous process both in oxidation and condensation phase. The AQ produced in Europe is manufactured with this method and the purity of the final product is minimum 98,5%, typical 99,2% and the AQ product is free from mutagenic substances, see Attachment 1: GC Analysis of Anthraquinone produced with vapor phase oxidation method.

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This process should not be mistaken for the process which involves oxidation of anthracene in Nitric acid.

AQ used in NTP 2005 study
The AQ used in the NTP 2005 study [NTP, 2005] was purchased from Zeneca Fine Chemicals and produced with nitric acid oxidation of anthracene and was contaminated with 9 nitro anthracene. AQ manufactured with this method consists of the mutagenic impurity 9-nitro anthracene. The nitric acid oxidation method is no longer used for production of AQ

Function of AQ in the pulp manufacturing process.
AQ works as a catalyst in the cooking process. AQ reduces the peeling break down reactions of the carbohydrates. AQ also increase the delignification rate. The results are an increased wood yield, a reduced need of alkali and sulfides for the delignification and reduced temperature needed for the cooking. The main benefits are:

- Less need of wood to produce the pulp
- Less need of cooking chemicals which reduce the load of the recovery plant
- Increased strengths properties of the pulp
- Energy savings, due to reduced temperature and need of alkali

For more details, see Attachment 2, Anthraquinone: An important additive for pulp manufacturer

Environmental benefits of AQ in the pulp manufacturing process.
The increase in yield and reduction of load has a direct positive impact on our environment by reduced consumption of wood and pulping chemicals. In the Nordic countries only, AQ saves several million trees every year, resulting in a positive impact to the environment through less fuel needed for the wood transports and reduced CO2 emissions. The saved trees will instead contribute to the absorption of CO2

A single pulp and paper industry which produces 350 000 Adt pulp per year, reduces the wood consumption in the range of 360 000 trees per year and substantial environmental benefits due to reduction of truck transports, fuel and CO2 emissions. The yearly savings will be:

1600 truck transports of wood
35 truck transports of fuel
195 m3 fuel
650 tons CO2

For more details, see Attachment 2, Anthraquinone: An important additive for pulp manufacturer

References not included in the CLH report

ECHA, 2013. Carcinogenicity. In: Guidance on the Application of the CLP Criteria. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. Version 4.0. November 2013 pp 319-412.

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References in Attachment 2. “Antraquinone: An important additive for pulp manufacturer” which are not included in CLH report

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B Comments regarding Toxicity

According to animal test data, AQ show no acute and only minimal toxicity. NTP 2005 study [NTP, 2005] indicated early small effects on feeding and weight development in the 14 weeks and 2 years studies. Final animal weight did not differ between exposed and control. Survival was similar between exposed and control animals. The NTP 2005 study were in accordance with the Bayer studies [Bayer AG, 1976] and [Bayer AG, 1979] that are cited in the CLH-report.

C) Comments regarding Mutagenicity

1. AQ without impurity of 9 nitro anthracene is not mutagen

Based on the references in the CLH report [Butterworth, 2001], [NTP, 2005], it’s clear that AQ without mutagenic impurities (9 nitro anthracene) or AQ with high purity was not mutagen in the test system used. The results of tests for AQ with the impurity 9-nitro anthracene vary from none to a dose dependent mutagenicity. Thus, this clearly

indicates that the AQ sample used by the NTP 2005 study may be affected by an unknown pattern of toxic impurities.

2. Mutagenicity of 9 nitro anthracene is proven
All studies referred in the CLH report regarding mutagenicity of 9 nitro anthracene was weakly positive to positive [Butterworth, 2004], [Fu et al, 1985], [NTP, 2005], [Pitts 1982], [Zeiger 1988] and [Durant, 1996]. An additional mutagenicity study performed by [Delgado-Rodriques et al, 1995], which is not cited in the CLH report, also reported a mutagenic potential of 9 NA in bacteria assay, a mammalian cell line and a Drosophila wing spot mutagenicity assay.

3 The degree of mutagenicity of 2-Hydroxi AQ is not fully verified
Butterworth et al reported that the mutagenicity of 2-hydroxi AQ was negative, while that of 9-nitro anthracene as positive [Butterworth et al: international Journal of Toxicology, 2004]. This outcome contradicts the description from "4.10.4 Summary and discussion of carcinogenicity" CLH report p.54, "Butterworth et al, 2004 estimated that 2-OH-AQ is a bacterial mutagen twice as potent as the impurity 9-NA "

4. Question marks regarding the formation of the metabolites 1-hydroxi AQ and 2-hydroxi-AQ.
The mutagenicity of the mother compound depends on the biotransformation to metabolites, of which 1-hydroxy-AQ and 2-hydroxy-AQ are debated in both CLH report and the NTP study. As shown by [Sato et al. ,1956] the isolation of 1-hydroxy-AQ was not successful, and the 2-hydroxy-AQ was interpreted as a major metabolite of AQ in rat urine present in low levels compared to the AQ-dose given in the diet, but only after air/oxygen contact in the chromatography process used for identification purposes. Later work [Sato et al., 1959], rats fed AQ and receiving an i.c. 35SO4-injection, indicated that 2-hydroxy-AQ was liberated from a ''substance'' in urine and concluded that the substance was a sulfate conjugate of 2-hydroxy-AQ.

The presence of this sulfate-2-hydroxy-AQ conjugate was not considered in the CLH or NTP-reports.

D) Comments regarding Carcinogenicity

The CLH report proposal for CLP classification of AQ as category 1B carcinogen, H 350 (May cause cancer) are mainly based on three main factors:

1. Results from the NTP study
2. That the metabolite 2-hydroxi-AQ is formed in high content
3. That the metabolite 2-hydroxi-AQ is much more mutagen than the impurity 9-nitro anthracene

According to our research the facts are not correct and its contradictions in the literature. It is major doubts regarding all three factors, se detailed comments below.

1) AQ used in the NTP study was consisting of mutagenic impurities. The results of tests for AQ with the impurity 9-nitro anthracene vary from none to a dose dependent mutagenicity [Butterworth, 2001], [NTP, 2005]. Tests with AQ without mutagenic impurities (9 nitro anthracene) or AQ with high purity was not mutagen in the test system used. Thus, this clearly indicates that the AQ sample used by the NTP study may be affected by an unknown pattern of toxic impurities.

It's not a clear link between the Substance AQ and the carcinogenicity.
The production samples of AQ used in the NTP 2005 study containing 9-nitro anthracene resulted in carcinogenic activities in rat and mouse [NTP, 2005]. This has been an important argument in the CLH proposal to suggest AQ in Category 1B with the hazard phrase "H350: May cause cancer". According to the CLP-regulation it is correct to use animal data on carcinogenicity for this category ''if there is a clear link between the substance and the carcinogenicity" [ECHA, 2013]. However, there are impurities involved here which implies there is not a clear link for 'one' substance to the toxic effects. In the NTP study it has not been fully investigated what role in the observed effects the impurities may have.

The AQ used in the NTP study was produced by the nitric acid production method which no longer are used. The AQ used today don't consist of any mutagenic impurities as 9-nitro anthracene. The AQ produced in Europe today are manufactured with the vapor oxidation process and has a purity of typically 99,2 % without any mutagenic impurities.

2) Formation of 2-hydroxi-AQ is not verified. In the discussion for carcinogenicity the CLH report says that the 2-hydroxi-AQ is the primary metabolite and that this substance is much more mutagen and therefore contributing more to cancer compared with 9-nitroanthracene. In fact shown by Sato et al. (1956) the isolation of 1-hydroxy-AQ was not successful, and the 2-hydroxy-AQ was interpreted as a major metabolite of AQ in rat urine present in low levels compared to the AQ-dose given in the diet, but only after air/oxygen contact in the chromatography process used for identification purposes. Later work [Sato et al., 1959], rats feed with AQ and receiving an i.c. 35SO4-injection, indicated that 2-hydroxy-AQ was liberated from a ''substance'' in urine and concluded that the substance was a sulfate conjugate of 2-hydroxy-AQ. The fact that the formation of 2-hydroxi is very low, the argumentation in both NTP 2005 and CLH reports regarding the contribution of this metabolite for the carcinogenicity of AQ are not correct. Sato el al 1959 was not cited in neither the NTP study nor CLH reports.

The presence of this sulfate-2-hydroxy-AQ conjugate was not considered in the CLH or NTP-reports

No studies are done of the biotransformation of AQ to metabolites 1-hydroxi-AQ and 2-hydroxi-AQ. Nor publications reporting that AQ is bio transformed to 1-hydroxy-AQ and 2-hydroxy-AQ in humans.

3) The grade of mutagenicity of 2-hydroxi-AQ is not fully verified. Butterworth et al reported that the mutagenicity of 2-hydroxi-AQ was negative, while that of 9-nitro

anthracene as positive [Butterworth et al: international Journal of Toxicology, 2004]. This outcome contradicts the description from “4.10.4 Summary and discussion of carcinogenicity” CLH report p.54, “Butterworth et al, 2004 estimated that 2-OH-AQ is a bacterial mutagen twice as potent as the impurity 9-NA “

Difference between IARC classification and CLH report proposal of CLP classification
The CLH-classification of AQ also goes beyond the IARC expert classification. In contrast, the IARC classification of AQ is in IARC-Group 2B: “Possibly carcinogenic to human” [IARC Monograph, 2012]. This reflects that this international expert organ on cancer issues, finds the available data less convincing for the mother substance AQ to be classified in Group 2A: “Probably carcinogenic to humans”. The distinction between the terms “possibly” and “probably” is important and means that there are doubts about the carcinogenicity of AQ in humans.

Conclusion
Based on the comments above Wibax AB cannot agree on the CLH reports proposed 1B, H350 “May cause cancer) classification for AQ

Attachments

Attachment 1. GC Analysis of Anthraquinone produced with vapor phase oxidation method

Attachment 2. Anthraquinone: An important additive for pulp manufacturer

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