CHPA

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Re: CHPA's proposal of limit for the process degradant 4-aminophenol

Dear members of the FDA/ USP/ CHPA Planning Committee on USP Monograph Modernization,

The Consumer Healthcare Product Association (CHPA) and its members, the manufacturers and developers of over-the-counter (OTC) medicines, recognize the need for modernization of U.S. Pharmacopeia (USP) monographs. CHPA member companies are dedicated to fulfilling their commitment outlined in the letter to this Planning Committee on February 2, 2011.

CHPA's Acetaminophen Degradant Working Group has committed to propose degradant standards in a prioritized approach. Our mission includes a first phase proposal of modernized monographs that specify 4-aminophenol limits and a general chapter on 4-aminophenol, a degradation product formed by hydrolysis of acetaminophen. Recently, this CHPA working group met and aligned on conservative limits appropriate for 4-aminophenol which are included below. The value CHPA is proposing will be included in its future general chapter submission and are based on data collected from CHPA member companies within the Acetaminophen Degradant Working Group that depicted ranges of degradant concentrations throughout the product shelf-life.

The supplemental table below was created to emulate USP's Acetaminophen Monograph Family Comparison Chart; the order and monograph names are identical to that of USP's chart. Several monographs (39%) are out of scope for the CHPA submission because they represent prescription dosage forms only; for example, monographs including the combination of acetaminophen with codeine (monographs 20-24 below) do not have a proposed limit from CHPA. The table also incorporates the CHPA proposed limit and the current corresponding USP or BP limits, where available.

CHPA is proposing that the percentage of 4-aminophenol (%w/w of Acetaminophen) in all existing dosage forms, including solids, oral solutions, oral liquids, and oral suspensions, should be "not more than 0.15%." In choosing this limit, the following was considered: risk assessment and toxicity of 4-aminophenol (see supplemetal document below), ICH Q3B guidelines, company data which is representative of achievable process capabilities, and the current British Pharmacopeia acetaminophen

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product monographs. The calculation and rationale are provided in the Consensus Toxicity Assessment of p-aminophenol (PAP), which can be found as a supplemental document in this letter.

CHPA member companies were eager to share these limits with this Planning Committee prior to the full submission to USP to increase the transparency of our process and progress.

Sincerely,

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Supplemental Table. *The Monographs within the Acetaminophen Monograph Family are listed with the corresponding limits (CHPA proposed, current USP, current BP).*

Monograph	4-aminophenol (% w/w)		
	Limit proposed	Current USP Limit	Current BP Limit
1. Acetaminophen	--	0.005	0.005
2. Acetaminophen Capsules	Not more than 0.15		
3. Acetaminophen Oral Solution	Not more than 0.15		Peds: not more than 0.5
4. Acetaminophen for Effervescent Oral Solution	Not more than 0.15		Soluble tablets- not greater than 0.1
5. Acetaminophen Suppositories	Not more than 0.15		not greater than 0.1
6. Acetaminophen Oral Suspension	Not more than 0.15	0.5	Pediatric: 0.1 Adult: 0.5
7. Acetaminophen Tablets	Not more than 0.15		not greater than 0.1
8. Acetaminophen Extended Release Tablets	Not more than 0.15		
9. Acetaminophen and Aspirin Tablets	Not more than 0.15		
10. Acetaminophen, Aspirin and Caffeine Tablets	Not more than 0.15		
11. Acetaminophen and Caffeine Tablets	Not more than 0.15		not greater than 0.1
12. Capsules Containing at Least Three of the Following: Acetaminophen, and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine	Not more than 0.15		
13. Oral Solution Containing at Least Three of the Following: Acetaminophen, and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine	Not more than 0.15		

14.	Tablets Containing at Least Three of the Following: Acetaminophen, and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine	Not more than 0.15		
15.	Capsules Containing at Least Three of the Following: Acetaminophen, and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine	Not more than 0.15		
16.	Oral Powder Containing at Least Three of the Following: Acetaminophen, and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine	Not more than 0.15		
17.	Oral Solution Containing at Least Three of the Following: Acetaminophen, and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine	Not more than 0.15		
18.	Tablets Containing at Least Three of the Following: Acetaminophen, and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine	Not more than 0.15		
19.	Acetaminophen, Chlorpheniramine Maleate, and Dextromethorphan Hydrobromide Tablets	Not more than 0.15		
20.	Acetaminophen and Codeine Phosphate Capsules	*not an OTC dosage*		
21.	Acetaminophen and Codeine Phosphate Oral Solution	*not an OTC dosage*		
22.	Acetaminophen and Codeine Phosphate Oral Suspension	*not an OTC dosage*		
23.	Acetaminophen and Codeine Phosphate Tablets	*not an OTC dosage*		
24.	Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution	Not more than 0.15		
25.	Acetaminophen and Diphenhydramine Citrate Tablets	Not more than 0.15		
26.	Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets	Not more than 0.15		
27.	Acetaminophen and Pseudoephedrine Hydrochloride Tablets	Not more than 0.15		
28.	Butalbital, Acetaminophen, and Caffeine Capsules	*not an OTC dosage*		
29.	Butalbital, Acetaminophen, and Caffeine Tablets	*not an OTC dosage*		
30.	Hydrocodone Bitartrate and Acetaminophen Tablets	*not an OTC dosage*		

31. Isometheptene Mucate, Dicloralphenazone, and Acetaminophen Capsules	*not an OTC dosage*		
32. Oxycodone and Acetaminophen Capsules	*not an OTC dosage*		
33. Oxycodone and Acetaminophen Tablets	*not an OTC dosage*		
34. Acetaminohpen and Tramadol Hydrochloride Tablets	*not an OTC dosage*	0.01	
35. Pentazocaine and Acetaminophen Tablets	*not an OTC dosage*		
36. Propoxyphene Hydrochloride and Acetaminophen Tablets	*not an OTC dosage*		
37. Propoxyphene Napsylate and Acetaminophen Tablets	*not an OTC dosage*		

Supplemental Document. *This Consensus Toxicity Assessment of p-aminophenol (PAP) document includes the calculation and rationale that led the Association to the proposed limit described in the body of this letter.*

Background

The Consumer Healthcare Products Association (CHPA) has been asked to propose a limit for para-aminophenol (PAP), a degradation product formed by hydrolysis of acetaminophen (APAP) OTC products. According to the results of some *in vitro* screening tests, PAP shows potential for clastogenic activity. Since subsequent *in vivo* studies qualified PAP as noncarcinogenic, the proposed limit for PAP in APAP is based on the margin of safety established by interpretation of the general toxicity profile of PAP.

As PAP is commonly used topically in cosmetic hair coloring products, the European Commission for Health and Consumer Protection directed the Scientific Committee on Consumer Products (SCCP) to evaluate and report on the safety of PAP. The SCCP Opinion on PAP, adopted in March 2005, hereafter called the SCCP Opinion on PAP, was the deliverable from that investigation, and it is incorporated by reference into this Assessment.

The SCCP Report on PAP provides summaries of ninety-six references of both published and unpublished studies conducted in humans, laboratory animals and *in vitro* test models. A committee of SCCP experts assessed the credibility and integrity for each study, based on peer review and audits, including for example, GLP compliance status, PAP test substance qualification (purity), adherence to standard protocols, etc. Because of the credibility and thoroughness of the SCCP Opinion on PAP and the expert review of the methodology and integrity of each study, the SCCP Opinion on PAP serves as the basis for this Toxicity Assessment by the CHPA Working Group on APAP.

Carcinogenicity Studies

PAP has been shown to be possibly clastogenic, based on results from *in vitro* test models and high dose exposure in laboratory animals. Studies in the rat suggested a threshold for genotoxicity since repeated administration of moderate oral doses of PAP did not induce chromosomal effects while a single, high oral dose may possibly have caused clastogenic effects. The reviewer is referred to citations Col. 91 and 92 in the SCCP Opinion on PAP for further detail.

The SCCP Opinion on PAP contains summaries of several chronic *in vivo* carcinogenicity studies: one by oral gavage in the rat (Col. 93), one by topical administration in the rat (Col. 72) and two by topical administration in the mouse (Col 7 and 8).

The oral gavage study in the rat (Col. 93) seemed particularly relevant to the issue of the acceptable concentration of PAP in orally administered APAP. Therefore, the full, original report (Report No. 11902

TCR 95/2/023 1/1998: P-Aminophenol – Potential Carcinogenic effects by Oral Gavage in Rats), hereafter called the CIT Two Year Carcinogenicity Study, is incorporated by reference. A summary of the study is located in the SCCP Opinion on PAP (Col.93).

According to the SCCP Opinion on PAP, factors which support the credibility and integrity of the CIT Two Year Carcinogenicity Study include:

- Conducted at the Centre International de Toxicology, Evreux, France
- Protocol was compliant with the Organisation for Economic Co-operation and Development (OECD), Draft Guideline for the Testing of Chemicals Number 451: Carcinogenicity Studies
- Conducted under and verified to comply with GLP requirements

In the study, dose levels of 2, 5, 12, and 30 mg/kg/day were selected on the basis of the results of a preliminary 13-week toxicity study in rats where daily oral doses of 30 and 100 mg/kg/day produced minimal to marked tubular nephrosis associated with marked tubular basophilia, respectively. Therefore 30 mg/kg/day was considered to be a potential Maximal Tolerated Dose (MTD) in the rat. The lower dose levels were included in order to determine a no effect level for potential toxic effects.

The test substance, 4-aminophenol, (PAP) was administered by daily gavage for at least 101 weeks to Sprague-Dawley rats at 2, 5, 12 and 30 mg/kg/day. Principal effects in this study were observed at 30 mg/kg/day and included a slightly lower survival rate in females and orange-colored urine which was attributed to urinary elimination of the test substance or its metabolites. The test substance showed neither a carcinogenic potential, nor an effect on the incidence of spontaneously occurring tumors at any dose-level.

The SCCP panel reviewing the CIT Two Year Carcinogenicity Study, concluded that: "The number of animals with more than one primary neoplasm and the number of benign and malignant tumours were comparatively similar in all groups including the control group, except for a marginal increase in the number of malignant lymphoma in males given 30 mg/kg/d (3 cases of heterogenous malignant lymphoma compared to 1 in the control group and 1 in the low dose group). It was concluded that the test substance showed neither a carcinogenic potential nor an effect on the incident of spontaneously occurring tumours at any dose level."

In our review of the CIT Two Year Carcinogenicity Study we were concerned about the high level of in life mortality occurring in all study animal groups, including animals treated with placebo. However, it was found that, in a study published by Nohynek et. al., (1993), similar animals, maintained under similar conditions, administered no test substance, had a similarly high mortality rate. The authors attribute this finding to genetic and environmental conditions. *Overall, the survival in the study on PAP was typical for the survival of this strain of rat at the time when the study was performed. However, given that the survival rates in all groups were similar (particularly those in controls and high-dose groups) and all animals moribund or found dead were included in the histopathological evaluation, a relatively low survival rate should not affect the outcome or validity of a carcinogenicity study, where tumor incidence*

of all groups is compared side-by-side. In conclusion, the scientific data support the view that the relatively low survival rate should not affect the scientific validity of the study.

The other carcinogenicity studies included the SCCP Opinion on PAP are by topical administration in the rat (Col. 72) and two topical exposure studies in the mouse (Col 7 and 8). Although less relevant than results for the oral route of PAP administration used in the CIT Two Year Carcinogenicity Study, tumors were also not induced by chronic topical application of PAP.

Based on primarily the CIT Two Year Carcinogenicity Study and, to some degree, on other studies summarized in the SCCP Opinion on PAP, it is concluded that PAP is not carcinogenic.

General Toxicity Studies

Because of the route and duration of exposure, the CIT Two Year Carcinogenicity Study served as a key factor in establishing the NOAEL for orally administered PAP. According to SCCP reviewers, the study conformed to OECD Test Guideline 451: Carcinogenicity Studies. Specifically, gross and histopathologic examination of the lungs, livers and kidneys of all study animals for evidence of toxicity was included in the study.

Additional support for the NOAEL for PAP was derived from The SCCP Opinion on PAP which also summarizes ninety-two other studies, published and unpublished, from safety evaluations of PAP given at various doses by different routes of administration, in humans, *in vitro* models and several laboratory animal species. In general it may be seen that doses of tens of milligrams/kg are required to induce systemic toxicity. The reviewer is referred to the SCCP Opinion on PAP for further detail.

Risk Assessment and Acceptable Daily Intake for PAP Degradation Product

The traditional approach to determine the Acceptable Daily Intake (ADI) for a substance is to identify a NOAEL from animal or human studies and then to apply appropriate correction factors, based on the perceived robustness of the data (Baird, et al., 1996; Dourson et al., 1996; Gaylor et al., 1999; Lehman and Fitzhugh, 1954). The equation used to determine the ADI is:

ADI = (NOAEL) (BW) / (SF) (MF), when the NOAEL is in mg/kg/day and where:

Acronym	Definition
NOAEL	No-Observed-Adverse-Effect Level for the endpoint of concern
BW	Body weight, a human adult body weight range of 50 - 70 kg is adopted
SF	Composite safety factor for uncertainties in interspecies extrapolation of toxicity data.
MF	Modifying factor included in the equation to compensate for lack of or deficiencies in data or for potential bioaccumulation

The NOAEL for orally administered PAP in the rat, (determined in the CIT Two Year Carcinogenicity Study) is 12 mg/kg/day. The product of the following safety or uncertainty factors (total composite safety factor) is applied to this NOAEL to determine the ADI:

Safety Factor	Value	Comment
Interspecies extrapolation	10	The SF from allometric scaling for estimating human toxicity potential based on rat toxicity data, recommended in European Commission Registration, Evaluation, and Authorization of Chemicals (REACH) legislation, is adopted. It consists of an allometric scaling factor of "4," which is species specific to rats, and an uncertainty factor of "2.5" (residual uncertainty from the PK/PD parameter for any species), yielding the result of "10."
Interindividual variability	10	Adjustment for variability in response among humans
Route-to-route extrapolation	1	Oral study for oral administration of PAP (as a degradation product in APAP)
Modifying factor	1	Adjustment for length of study vs. chronic (2 yr) study
Total composite SF	**100**	**(10)(10)(1)(1)**

Calculation of the ADI by application of the safety and uncertainty factors to data for PAP yields the following result:

(1) ADI (in mg/kg of BW) = (NOAEL) / (SF)
(12 mg/kg) / (100) = 0.12 mg/kg

Thus, the ADI for a 50-70 kg human is calculated to be a range of 6 - 8.4 mg of PAP /day.

Recommended Safety Limit for PAP in APAP Products

Formula (2) represents the specified limit of PAP, based on ingestion of the maximum daily dose of APAP (4,000 mg) by a 50 kg adult.

(2) Safety Limit (% PAP in APAP) = (ADI $^{50\ kg\ adult}$ / Maximum Daily Dose of APAP $^{4000\ mg\ /day}$) x 100
(6 mg / day) / (4000 mg / kg) x 100 = 0. 15 % w/w

References

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