

Date: May 7, 2018

FREEDOM OF INFORMATION SUMMARY

IMPORT TOLERANCE

I. GENERAL INFORMATION

- A. **Established Name:** benzocaine
- B. **Food-Animal Species:** Atlantic salmon and rainbow trout
- C. **Tolerances/tissues:** 50 ppb benzocaine in muscle with adhering skin
- D. **File Number:** VMF 006-035
- E. **Petitioner:** ACD Pharmaceuticals

II. HUMAN FOOD SAFETY

A. Microbial Food Safety:

1. Antimicrobial Resistance:

Benzocaine does not share mechanisms of antimicrobial activity with antimicrobial drug classes. No data could be identified to support benzocaine-induced selection or co-selection of resistance to antimicrobial drugs considered important to human medicine. The use of benzocaine (BENZOAK) in Atlantic salmon and rainbow trout is not thought, and has not been reported to impact antimicrobial resistance among bacteria of public health concern in or on treated fish.

2. Impact of Residues on Human Intestinal Flora:

CVM concludes that there is no concern that benzocaine residues associated with imported Atlantic salmon and rainbow trout will affect the intestinal flora of human consumers in the U.S.; therefore, there is no need to determine an mADI for the compound.

B. Toxicology:

1. Summary of Toxicology Studies:

The toxicology information on benzocaine was obtained from the published scientific literature. Genotoxicity studies, an acute toxicity study in the rats, and human clinical studies reported from five key references are listed below:

a. Genotoxicity Studies

Brock, W.J., and Bell, T.A. The *in vitro* and *in vivo* genotoxicity of benzocaine: a brief communication. International Journal of Toxicology 31:222-227 (2012).

Benzocaine was not genotoxic in the bacterial reverse mutation assay, the *in vitro* mammalian cell mutagenesis assay in mouse lymphoma L5178Y cells, and the *in vivo* mouse micronucleus assay.

b. Acute Toxicity Study in the Rat

Von Tungeln, L.S., Zhou, T., Woodling, K.A., Doerge, D.R., Greenlees, K.J., and Beland, F.A. Benzocaine-induced methemoglobinemia in an acute-exposure rat model. Food and Chemistry Toxicology 49:2530-2535 (2011).

A no-observable-adverse-effect level (NOAEL) of 16 mg/ kg body weight was established based on no benzocaine-induced methemoglobinemia noted at this dose when given a single dose orally to Sprague-Dawley rats.

c. Human Clinical Studies

Novaro, G.M., Aronow, H.D., Militello, M.A., Garcia, M.J., Sabik, E.M. Benzocaine-induced methemoglobinemia: experience from a high-volume transesophageal echocardiography laboratory. Journal of the American Society of Echocardiography 16:170–175 (2003).

Chowdhary, S., Bukoye, B., Bhansali, A.M., Carbo, A.R., Adra, M., Barnett, S., Aronson, M.D., Leffler, D.A. Risk of topical anesthetic-induced methemoglobinemia: a 10-year retrospective case-control study. JAMA Internal Medicine 173:771-776 (2013).

Hersh, E.V., Ciancio, S.G., Kuperstein A.S., Stoopler, E.T., Moore, P.A., Levine, S.T., Casamassimo, P., Leyva, R., Mathew, T., Shibly, O., Creighton, P., Jeffers, G.E., Corby, P.M.A., Turetzky, S.N., Papas, A., Wallen J., Idzik-Starr, C., Gordon, S.M. An evaluation of 10 percent and 20 percent benzocaine gels in patients with acute toothaches: Efficacy, tolerability and compliance with label dose administration directions. J Am Dent Assoc. May; 144(5): 517–526 (2013).

Low incidences of benzocaine-induced methemoglobinemia in clinical practice were reported when humans were given benzocaine containing medicines (generally over-the-counter topical gel/liquid/spray with benzocaine doses ranging from 0.2% to 20%).

2. Margin of Exposure (MOE) Assessment:

An Acceptable Daily Intake (ADI) for chronic exposure to benzocaine residues could not be established based on insufficient information from the published literature. The Agency conducted a MOE assessment, which takes into consideration both the available toxicology information (including key scientific literature summarized above, two additional references listed below and long history of safety use of benzocaine in human medicines) and the estimated human dietary exposure to benzocaine residues at 50 ppb (see C.5. below). Taken together, with reasonable certainty, residue concentrations of parent benzocaine in fish muscle with adhering skin in natural proportions at or below 50 ppb are unlikely to pose human food safety concerns.

Batke, M., Escher S., Hoffmann-Doerr, S., Melber, C., Messinger, H., Mangelsdorf, I. Evaluation of time extrapolation factors based on the database RepDose. Toxicology Letters 205:122-129 (2011).

The ratio for extrapolation of NOAELs across subacute to chronic oral exposure was suggested to be of a value of 29.

Pohl, H.R., Chou, C.H., Ruiz, P., Holler, J.S. Chemical risk assessment and uncertainty associated with extrapolation across exposure duration. Regulatory Toxicology and Pharmacology 57:18-23 (2010).

The average ratios for extrapolation NOAELs across acute/intermediate duration and intermediate/chronic duration are 25.56 and 4.38, respectively.

C. Summary of Residue Chemistry Studies:

1. Total Residue and Metabolism Study

Total residue depletion and metabolic profile of selected drugs in catfish: benzocaine. Hayton, W., Szoke, A., Kemmenoe, B., Vick, A. (Study No. 725417-008, FDA Contract 223-91-7015 by the Ohio State University, College of Pharmacy, Columbus, OH, USA)

Parent benzocaine was found to be the dominant metabolite species in catfish.

2. Comparative Metabolism Study

Total residue depletion and metabolic profile of selected drugs in catfish: benzocaine. Hayton, W., Szoke, A., Kemmenoe, B., Vick, A. (Study No. 725417-009, FDA Contract 223-91-7015 by the Ohio State University, College of Pharmacy, Columbus, OH, USA)

The metabolic profile of benzocaine was similar in catfish and rat in that each metabolite identified in catfish also was present in the rat.

3. Tissue Residue Depletion Studies

Residue depletion data are not needed for establishing an import tolerance because a withdrawal period is not assigned. However, the studies listed below provide supporting information about the depletion of benzocaine from fish. Tissue residues immediately after exposure in both catfish and salmonids are all below 40 mg/kg (40 ppm) and then quickly deplete to ppb concentrations.

1. Stehly, G., Meinertz, J., Gingerich, W., Mazik, P., Gaikowski, M. "Effects of temperature on the loss of benzocaine and acetylated benzocaine residues from edible tissues of channel catfish *Ictalurus punctatus*." (FDA Contract 224-92-7036 by the National Biological Service, Upper Mississippi Science Center, La Crosse, WI, USA. Study No. CAP-94-00078-01)
2. Allen, J. "Residues of Benzocaine in Rainbow Trout, Largemouth Bass, and Fish Meal." *The Progressive Fish Culturist* 50:59-60 (1988).
3. Stehly, G., Meinertz, J., Gingerich, W. "Effects of temperature on the elimination of benzocaine and acetylated benzocaine residues from the edible fillet of rainbow trout (*Oncorhynchus mykiss*)."
Food Additives and Contaminants 17(5):387-392 (2000).

4. Target Tissue and Marker Residue Assignment:

The target tissue is muscle with adhering skin. The marker residue is parent benzocaine because this is the residue that is present in the highest concentration and persists for the longest period of time.

5. Tolerance Assignment:

We are establishing an import tolerance of 50 ppb, approximately twice the LOQ for the analytical method, for residues of parent benzocaine in the muscle with adhering skin of Atlantic salmon and rainbow trout.

6. Withdrawal Period:

A withdrawal period is not assigned when establishing an import tolerance.

D. Analytical Method for Residues:

An HPLC analytical method adequate for monitoring residues of benzocaine in fish muscle and skin in natural proportions exists. The LOQ for benzocaine was quantitated at 22 mcg/kg (22 ppb).

Meinertz, J., Stehly, G., Hubert, T., and Bernardy, J. "Liquid chromatographic determination of benzocaine and N-acetyl-benzocaine in the edible fillet tissue from rainbow trout." *Journal of Chromatography* 855 (1999): 255-260.

The method is on file with the Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855. To obtain a copy of the analytical method, please submit a Freedom of Information Summary request to: <https://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm>.

E. Conclusions:

The Center for Veterinary Medicine concludes that we have the appropriate information for us to assign an import tolerance for benzocaine in salmonids. We assign an import tolerance of 50 ppb benzocaine in muscle with adhering skin of Atlantic salmon and rainbow trout.

III. AGENCY CONCLUSIONS

These data support the establishment of an import tolerance of 50 ppb benzocaine in muscle with adhering skin of Atlantic salmon and rainbow trout as provided under Sec. 512(a)(6) of the Food, Drug, and Cosmetic Act.