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Dr. Robert P. Yunick
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Re: Isonox® 132--FDA Status for Use in Rigid PVC; Our File No. SC0854

Dear Bob:

In your letter of August 19, 1986 you requested our opinion regarding the Food and Drug Administration (FDA) status of Isonox 132 when used as an antioxidant in rigid polyvinyl chloride (PVC). Based upon the extraction data you provided with your letter, we have no hesitation in providing our opinion that the intended use of Isonox 132 may properly be said to be in compliance with the Federal Food, Drug and Cosmetic Act (Act) and the applicable Food Additive Regulations. The more detailed rationale for this opinion is as follows.

Legal-Regulatory Background

Before considering the specific status of the subject antioxidant, it may be useful to review the applicable legal principles involved here. As you know, section 201(s) of the Act defines a food additive, in pertinent part, as:

> [A]ny substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food . . . if such substance is not generally recognized . . . to be safe under the conditions of its intended use; except that such term does not include --
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> (4) any substance used in accordance with a sanction or approval granted prior to the enactment of this paragraph pursuant to this Act.

This definition is repeated in Section 170.3(e) of the Food Additive Regulations which adds, again in relevant part, the following explanatory information:

> A material used in the production of containers and packages is subject to the definition if it may reasonably be expected to become a component . . . directly or indirectly of food packed in the container . . . If there is no migration of a packaging component from the package to the food, it does not become a component of the food and thus is not a food additive.

Thus, a substance that is reasonably expected to become a component of food when employed in a food contact application must be (a) the subject of an applicable Food Additive Regulation, (b) the subject of a prior sanction or approval, or (c) deemed generally recognized as safe (GRAS). If the substance is not reasonably expected to become a component of food under the intended conditions of use, it is not a food additive, and it may be so employed without any prior action by or consultation with FDA.

FDA has not provided definitive objective crteria for determining when a substance in a food packaging material may reasonably be expected to become a component of food. Nevertheless, guidance is available from at least two different past occurrences.

The first event relates to the draft of a proposal circulated by FDA as its response to wide-spread criticisms offered by the food packaging industries at the National Conference for Indirect Additives held in Washington in February of 1968. This so-called "Ramsey proposal" would have acknowledged in a regulation the propriety of the use, without the prior promulgation of food additive regulations, of substances that contribute no more than 0.05 ppm (50 ppb) to contacted food, components of articles used in contact with dry, non-fatty food, and substances employed as components of articles intended for repeated use in contact with bulk quantities of food. This would have applied to all substances except those known to pose some special toxicological concern, e.g., a heavy metal, a known carcinogen, or something that produced toxic reactions at levels of 40 ppm or less in the diet of man or animals. We are enclosing a copy of this proposal for your ready reference. (Although never formally adopted, the standards were deemed scientifically acceptable.)

Further clarification of the meaning of the term "food additive" was provided by the United States Court of Appeals in Monsanto v. Kennedy, 613 F.2d 947 (D.C. Cir. 1979). In this case, FDA argued that any contact of a substance with food must result in some transfer to the food and thus made the substance at issue in the case, acrylonitrile/styrene copolymer, a food additive. The Court stated:

> Congress did not intend that the component requirement of a "food additive" would be satisfied by . . . a mere finding of any contact whatever with food . . . . For the component element of the definition to be satisfied, Congress must have intended the Commissioner to determine with a fair degree of confidence that a substance migrates into food in more than insignificant amounts.

613 F.2d 947, 948 (D.C. Cir. 1979).

Monsanto v. Kennedy has been cited as authority for the Food and Drug Administration's own adoption of what has come to be called the *de minimis* concept since 1979; i.e., FDA has used the case as support for decisions it has made that go so far as permitting carcinogenic substances to remain on the market where the amounts expected to become a component of food have been found to be of no toxicological significance. This was most recently evidenced by the Agency's decision to permit the continued use of methylene chloride, a known carcinogen, in decaffeinating coffee (50 Fed. Reg. 51551; Dec. 18, 1985). It is obvious that if the de minimis concept endorsed by the Court in Monsanto v. Kennedy is useful to FDA to justify permitting this use of a carcinogen in food, the de minimis doctrine must certainly be applicable to toxicologically innocuous, indirect additives.

Status of Isonox 132

With your letter, you provided results of extraction tests conducted on rigid PVC plaques containing known concentrations of Isonox 132. These tests involved exposing 35-mil plaques made with 900 and 1800 parts per million (ppm) of Isonox 132 to n-heptane at 120°F for 10 hours. At the end of this time, the solvent was concentrated under a nitrogen stream, made up to a known concentration, and analyzed by gas chromatography/flame ionization detection (GC/FID) spectrometry. No Isonox 132 was detected in the solvent. Because n-heptane as a fat-simulant is a far more aggressive extractant than water, this same "not-detected" conclusion can be applied to aqueous extractants.

Additional tests were conducted by adding known quantities of Isonox 132 to the test solution and analyzing by the same GC/FID method to determine the sensitivity and recovery of the method. In this way, it was determined that the lower limit of sensitivity of the analytical method was equivalent to approximately 4 ppb of Isonox in the solvent, after applying a correction factor of 5 in accordance with accepted FDA practice for heptane extraction data. Moreover, validation studies carried out with known concentrations of Isonox 132 in the solvent demonstrated a high level of recovery for the analytical method. On the basis of these data, it is

apparent that when used as described to us, Isonox 132 may not reasonably be expected to become a component of food. Thus, we have no hesitation in providing our opinion that Isonox 132 may be used in rigid PVC and that such use may properly be said to comply with the Act and all applicable FDA Regulations.

Our comfort factor in providing this opinion is increased by the knowledge that Isonox 132 is currently regulated for use in food packaging adhesives at 21 C.F.R. § 175.105 and by the fact that the antioxidant is known to be of a low order of toxicity. These factors add to the assurance that any minute, undetected quantity of Isonox 132 that might conceivably enter the diet from the use of the additive in PVC would certainly be generally recognized as safe.

We trust you will find this letter fully responsive to your request for our assistance. Should any questions remain, or if we may be of help in any other way, please do not hesitate to let us know.

Cordially yours,

Jerome H. Heckman