FOOD SAFETY

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Polyvinylpyrrolidone

Summary

Food Safety Commission of Japan

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of 'polyvinylpyrrolidone' (CAS number: 9003-39-8), a food additive used for producing foods in capsules and/or tablet form, based on data from various studies. The food additive 'polyvinylpyrrolidone' (hereinafter referred to as 'this additive') contains polyvinylpyrrolidone (hereinafter referred to as 'PVP') as well as the residual monomer, 1-vinyl-2-pyrrolidone (hereinafter referred to as 'NVP') and hydrazine as impurities. FSCJ considered that PVP taken orally is barely absorbed from the digestive tract and is directly excreted into feces, based on toxicokinetic studies done on experimental animals. According to case reports available, oral intake of pharmaceutical products containing PVP seldom but evidently cause allergic reactions in humans. Allergenicity of PVP thus cannot be ruled out, but these reports on allergenicity lacked any information on doses; FSCJ therefore does not neglect the possibility that PVP potentially acts as a sensitizer in a limited population through unidentified mechanisms. Therefore, FSCJ deemed that most of the allergic reactions observed after oral intake of PVP might be attributable to sensitization caused by topical or other application of povidone-iodine. It deemed that the probability of sensitizing through oral intake of PVP alone is extremely low. FSCJ concluded that NVP is of no concern for genotoxicity, acute toxicity and repeated dose toxicity on human health. Therefore FSCJ considered that the carcinogenicity of NVP manifested due to a mechanism other than a genotoxic one. FSCJ concluded that it is difficult to assess the carcinogenicity based on the amount of intake of NVP included in this additive. Regarding the safety of hydrazine, carcinogenicity and genotoxicity have been reported. FSCJ thus concluded that the no-observed-adverse-effect level (NOAEL) cannot be established. Based on the quantitative carcinogenic risk assessments of hydrazine performed in the United States and Europe, and based on the amount of hydrazine contained (500 ppb at the highest estimate), FSCJ estimated the carcinogenic risk level of humans exposed to this additive at an estimated daily intake (480 mg/person/day) in Japan. Consequently the risk level was estimated to be 9.0×10^{-7} (about 1.1 millionths). This estimated risk level is smaller than one-in-a-million, which is generally considered negligible as a genotoxic carcinogenic risk level. The risk is thus considered extremely low. FSCJ concluded that consumption of hydrazine contained in this additive does not pose safety concerns for the consumers. Based on the above findings, this additive is considered to be of no concern for food safety as long as used appropriately as a food additive, and FSCJ concluded that it is unnecessary to specify the acceptable daily intake (ADI). The risk management agency thus must take appropriate measures to prevent development of allergy upon use of this additive. Regarding hydrazine, the risk management agency must continue to commit itself to reduce the risk to a technically feasible level.

Conclusion in Brief

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of 'polyvinylpyrrolidone' (CAS number: 9003–39-8), a food additive used for producing foods in capsules and/or tablet form, based on data from various studies. The food additive 'polyvinylpyrrolidone' (hereinafter referred to as 'this additive') contains polyvinylpyrrol-

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idone (hereinafter referred to as 'PVP') as well as the residual monomer, 1-vinyl-2-pyrrolidone (hereinafter referred to as 'NVP') and hydrazine as impurities. The data used in the assessment are on; the genotoxicity, repeated dose toxicity, carcinogenicity and reproductive and developmental toxicities of PVP, NVP and hydrazine as test substances. FSCJ considered that PVP taken orally is barely absorbed from the digestive tract and is directly excreted into feces, based on toxicokinetic studies done on experimental animals.

According to case reports available, oral intake of pharmaceutical products containing PVP seldom but evidently cause allergic reactions in humans. Allergenicity of PVP thus cannot be ruled out. None of these reports on allergenicity included any information on doses; FSCJ considered it difficult to determine the allergy-inducing dose. Reports denying the sensitizing action of PVP are available, but others demonstrated production of PVP-specific IgE antibodies in some cases. FSCJ therefore does not neglect the possibility that PVP potentially acts as a sensitizer in a limited population through unidentified mechanisms. Toxicokinetics data, however, suggested the scarce oral availability of PVP. In addition, no information is available on sensitization induced by oral intake of PVP. Therefore, FSCJ deemed that most of the allergic reactions observed after oral intake of PVP might be attributable to sensitization caused by topical or other application of povidone-iodine. It deemed that the probability of sensitizing through oral intake of PVP alone is extremely low. Moreover, FSCJ concluded that PVP is of no concern for genotoxicity, acute toxicity, chronic toxicity, carcinogenicity and reproductive and developmental toxicity, on the basis of the available toxicological data.

Taking into account the safety data of NVP, the draft standards for this additive (0.001% or lower for NVP) and the estimated daily intake (480 mg/person/day) after its approval in Japan, FSCJ concluded that NVP is of no concern for genotoxicity, acute toxicity and repeated dose toxicity on human health. With regard to the carcinogenicity of NVP, oral administration studies have not been conducted. Although the inhalation exposure study showed NVP's carcinogenic activities on the upper respiratory tract and the liver, genotoxicity of NVP has not been reported. Therefore FSCJ considered that the carcinogenicity manifested due to a mechanism other than a genotoxic one. Although carcinogenic risk of NVP upon oral exposure cannot be excluded, it is difficult to determine the carcinogenic dose. FSCJ concluded that it is difficult to assess the carcinogenicity based on the amount of intake of NVP included in this additive. Regarding the safety of hydrazine, carcinogenicity and genotoxicity have been reported. Based on these findings, FSCJ considered that the involvement of genotoxic mechanisms in its carcinogenicity cannot be ruled out, and thus concluded that the no-observed-adverse-effect level (NOAEL) cannot be established.

Based on the quantitative carcinogenic risk assessments of hydrazine performed in the United States and Europe, and based on the amount of hydrazine contained (500 ppb at the highest estimate), FSCJ estimated the carcinogenic risk level of humans exposed to this additive at an estimated daily intake (480 mg/person/day) in Japan. Consequently the risk level was estimated to be 9.0×10^{-7} (about 1.1 millionths). This estimated risk level is smaller than one-in-a-million, which is generally considered negligible as a genotoxic carcinogenic risk level. The risk is thus considered extremely low. FSCJ concluded that consumption of hydrazine contained in this additive does not pose safety concerns for the consumers.

Based on the above findings, this additive is considered to be of no concern for food safety as long as used appropriately as a food additive, and FSCJ concluded that it is unnecessary to specify the acceptable daily intake (ADI). Although rare, sensitization to PVP is inducible through topical application of povidone-iodine, etc., and the risk of anaphylaxis remains in sensitized population. Moreover, it is difficult to identify the threshold based on the currently available data. The risk management agency thus must take appropriate measures to prevent development of allergy upon use of this additive. Regarding hydrazine, the risk management agency must continue to commit itself to reduce the risk to a technically feasible level.