Risk Assessment of Carcinogens: A New Approach Based on Scientific Evidence

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Summary

A low-dose carcinogenic risk of various environmental carcinogens was analysed by using medium-term rat tests for carcinogens on the basis of "weights of evidence."

1. Low-dose carcinogenicity of genotoxic carcinogens

One of the heterocyclic amines, 2-amino-3,8-dimethylimidazo [4,5-*f*]quinoxaline (MeIQx), was orally administered to 21-day-old male rats for a maximum period of 32 weeks. The incidence of glutathione *S*-transferase placental form (GST-P) positive foci, which are the endpoint maker and considered preneoplastic lesions in rat hepatocarcinogenesis, was not increased at 0.001 to 1 ppm, but tended to rise at 10 ppm, and was elevated at 100 ppm. Adducts of MelQx with DNA were formed by exposure of an extremely low dose of the chemical, while the 8-hydrodeoxyguanosine (8-OHdG) formation was increased at 0.1 ppm or higher doses. Furthermore, when MeIQx was administered to local gene-introduced transgenic rats, namely Big Blue rats, the mutation frequency of Local gene was elevated at 10 ppm or higher, while the GST-P positive foci formation was increased at 100 ppm. The mutation rate of H-ras gene was induced by administration of 10 ppm or higher doses of MeIQx. In case of administration to rats a nitroso-compound, diethylnitrosoamine, incidences of hepatic GST-P positive foci and lacI gene mutation frequencies were similar to the case of MeIQx. Furthermore, in experiment with a heterocyclic amine, amino-1-methyl-6-phenylimidazo [4,5-*b*]pyridine (PhIP), its low dose carcinogenicity in the colon was examined after administration to rats in the diet for 16 weeks. The incidence of aberrant crypt foci, which are the marker in colon carcinogenesis, was increased only at high doses, while the PhIP-DNA adduct was noted from a low dose. Kidney carcinogenicity of potassium bromate was investigated in rats by the medium-term tests. Increase in mutation frequency of local gene as well as occurrence of kidney tumors were observed only at high doses.

2. Low-dose carcinogenicity of non-genotoxic carcinogens

Low-dose carcinogenicity of Phenobarbital (PB) was studies by a rat liver medium-term assay for carcinogens (Ito-test). Dose-dependent increase of GST-P positive foci incidences was observed in the liver of 60 to 500 ppm PB-treated rats, however, at low-doses of 1 to 7.5 ppm they were decreased as compared with the control group (J-curve, homesis phenomenon). Similar results

were obtained regarding rat hepatocarcinogenesis in experiments with alpha-benzenehexachloride (α-BHC) and 1,1-bis(*p*-chlorophenyl)-2,2,2-trichloroethane (DDT).

3. Conclusions

Genotoxic carcinogens were concluded to have a threshold, at least a practical threshold in carcinogenesis, and risk management from this point of view is desired. Also in the case of non-genotoxic carcinogens, the presence of a threshold was proven. On the basis of these findings, this lecture is intended to propose a new approach to risk assessment and risk management of carcinogens.