This is a provisional English translation of an excerpt from the original full report.

Risk Assessment Report

Di-n-octyl phthalate (DNOP)

(Apparatuses, Containers and Packages)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

FSCJ conducted a risk assessment of di-n-octyl phthalate (DNOP) (CAS No. 117-84-0) for the revision of the standards and criteria for apparatuses, containers and packages.

The data used in the assessment include pharmacokinetics (rats, baboons, ferrets, and human), acute toxicity (mice, rats and guinea pigs), subacute toxicity (mice and rats), chronic toxicity and carcinogenicity (mice and rats), reproductive and developmental toxicity (mice and rats), genotoxicity, among others.

In animal studies available, DNOP demonstrated low acute toxicity. Subacute toxicity and combined chronic toxicity/carcinogenicity studies showed that the liver was a major target of DNOP. In developmental toxicity studies, increased accessory 14th ribs in fetuses were observed, while DNOP showed no effect on reproductivity. FSCJ concluded that DNOP has no carcinogenicity relevant to human health based on the results from carcinogenicity study.
DNOP has no genototoxicity relevant to human health based on the results from genotoxicity studies, and FSCJ considered it possible to establish a torelable daily intake (TDI) in the assessment.

Reports are available from epidemiological studies where MCPP, a main metabolite of DNOP in urine, was taken as a DNOP exposure index. However, FSCJ could not reveal the effects of DNOP exposure on human health based on currently available epidimeological data, because MCPP is also a metabolite from other phthalate esters such as DBP.
Hence, FSCJ considered it appropriate to specify the TDI based on the results of various animal studies.

Among various studies on subacute toxicity, chronic toxicity/carcinogenicity, reproductive and developmental toxicity of DNOP, the lowest no-observed-adverse-effect level (NOAEL) was obtained in a 13-week subacute toxicity study in rats conducted by Poon et al. (1997). Perivenous cytoplasmic vacuolation

accompanied by an increased hepatocellular cytoplasmic volume was observed in males and females administered with 350.1 and 402.9 mg/kg bw/day, respectively. Therefore, FSCJ concluded that the NOAELs of the said study are 36.8 and 40.8 mg/kg bw/day for males and for females, respectively.
The lowest value of lowest-observed-adverse-effect level (LOAEL) in the toxicological studies was LOAEL of 113 mg/kg body weight/day in a 2-year combined chronic toxicity/carcinogenicity study in mice (Wood et al., 2014). Because cytoplasmic alteration in hepatocytes and hepatocellular hypertrophy were observed at this LOAEL, FSCJ could not establish a NOAEL for this study.

Because common ratio in the studies by Poon et al. (1997) was big, and because the lowest value of LOAEL has been obtained in a study for the longer period, a 2-year combined chronic toxicity/carcinogenicity study in mice (Wood et al., 2014), though a NOAEL could not be obtained, FSCJ concluded to establish the TDI of DNOP based on the results from the said study.

The cytoplasmic alteration in hepatocytes and hepatocellular hypertrophy observed at the dose of 113 mg/kg bw/day were without any change in the organ weight, and the incident rate and severity of the hepatocellular hypertrophy observed in the period from 80 to 104 weeks did not increase in a dose dependent manner. In addition, the cytoplasmic alteration in hepatocytes was observed even in the control animals after 60 weeks, without any significant difference from 80 to 104 weeks. Consequently, FSCJ concluded that the NOAEL can be extrapolated from the LOAEL dividing it by 3, considering the said alteration mild.
Given the uncertainty factor of 3 for the extrapolation from LOAEL to NOAEL, TDI of 0.37 mg/kg bw/day is specified. Meanwhile, NOAEL was not obtained in the developmental toxicity study (Saillentfait et al., 2011) because increased accessory 14th ribs in fetuses were observed even at the lowest dose of 250 mg/kg bw/day. FSCJ considered this accessory 14th ribs in fetuses observed at the LOAEL of 250 mg/kg bw/day mild, because it was naturally occurring in rats, and the increase in the occurrence rate per litter at the LOAEL was not significantly different from that in the control animals. As the result, a TDI of 0.83 mg/kg bw/day was induced by the extrapolation from LOAEL at the said study to NOAEL applying the uncertainty factor of 3, and 0.37 mg/kg bw/day was found to be lower.

In conclusion, FSCJ specified the TDI of 0.37 mg/kg bw/day by applying Uncertainty Factor of 300 (10 for species difference, 10 for individual difference, and additional 3 for the use of LOAEL) to the LOAEL (113 mg/kg bw/day) observed in the study by Wood et al. (2014).