A Cancer Risk Assessment on ingestion of cow milk and powered milk contaminated by Di(2-ethylhexyl)Phthalate in Korea

Shinai Choi, Youn-Seok Kang, Tae-Hwa Nah, Chang-Hwan Oh,
Hyomin Lee*, Jongsei Park

LabFrontier, Co. Ltd., KSBC Bldg, #Mt. 111-8, Iui-dong, Paldal-ku, Suwon, Kyonggi-do 442-270, Korea,
*Division of Risk Assessment, National Institute of Toxicological Research,
#5 Nokbun-dong, Eunpyung-ku, Seoul 122-704, Korea

Introduction

The United States Environmental Protection Agency(EPA) characterized the cancer hazard of di(2-ethylhexyl)-phthalate(DEHP) as a B2 group(probable human carcinogen) and proposed new guidelines for carcinogen risk assessment. This proposed guidelines state that "If in a particular case, the evidence indicated a threshold, as in the case of carcinogenicity being secondary to another toxicity that has a threshold, the margin of exposure analysis for toxicity is the same as is done for a non-cancer endpoint". DEHP is excellent candidate for reconsideration under the new guidelines for carcinogen risk assessment.

Material and Methods

This study is conducted risk assessment for infant exposure on DEHP in powdered milk and lifetime exposure on DEHP in cow milk using methodology suggested EPA's new guideline on carcinogenic risk assessment and current methodology.

Current methodology uses cancer potency which is slop factor of dose-response curve identified by mathematical model. Using cancer potency is 1.4 10^{-2}(mg/kg/day)$^{-1}$ proposed by U.S.EPA, it is depends on the mouse liver data from NTP bioassay(NTP, 1982).

The new guidelines allow methodology more appropriate to chemicals acting through threshold-based, non-genotoxic mechanisms when, indeed, sufficiently strong supportive evidence exists.

The nonlinear approach advocated in the proposed guidelines is the MOE, which is defined in the guidelines as the LED10(or other point of departure, such as NOEL) divided by environmental exposure of interest.

Based on the established association of DEHP-induced rodent liver cancer with a receptor-med

iated mechanism and general scientific consensus that receptor mechanism involve dose thresh olds(Poland, 1997), it is concluded that risk assessment with DEHP can most appropriately be conducted using the MOE approach. Estimation of MOE value is based on the mouse NOE L for peroxisome proliferation (20 mg/kg B.W).

Results

Calculation of Human Exposure Dose

Exposure scenario is ingestion of powdered milk from birth to 2 years old and daily ingestio n of 200ml(1 pack) cow milk from 2 years old to death as end time of lifetime assumed 70 years. Lifetime average daily dose(LADD, mg DEHP/kg B.W./day) is calculated as intake dos e through ingestion of powdered milk and cow milk contaminated by DEHP applying Monte-Carlo Method by Crystal Ball.

DEHP pollution data is fitted to log-normal distribution which is known as most environmenta l pollution data.

Calculated LADD for infant exposure on powdered milk is 8.11 10^{-4}(mg/kg/day) as mean, 1. 76 10^{-3} as the 95th percentile value. Total LADD for lifetime exposure on powdered milk a nd cow milk is 2.02 10^{-3} as mean, 3.92 10^{-3} as the 95th percentile value

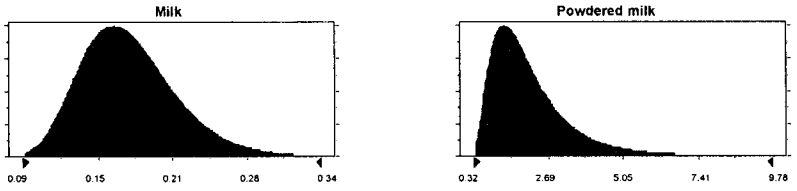

Fig 1. Distribution of DEHP level in cow milk and powdered milk .

Estimation of Cancer Risk and MOE

Estimated cancer risk(using cancer potency : 1.4 10^{-2}(mg/kg/day)$^{-1}$) of infant exposure on po wdered milk is 9.71 10^{-6}, of lifetime exposure on powdered milk and cow milk is 2.85 10^{-5}. Estimated MOE(using selected NOEL 20mg/kg/day from David et al.(1997) of infant expos ure on powdered milk is 34022, of lifetime exposure on powdered milk and cow milk in 120 02. Total cancer risk and total MOE is aggregated each cancer risk and MOR in exposure o f cow milk and powdered milk.

The 95th percentile(upper) value of total cancer risk is 5.53 10^{-5} and the 5th percentile(lower) total MOE is 5097. This value is estimated by Monte-Carlo simulation using Crystal Ball(De

cisioneering Co., 2001).

A commonly used default MOE of 100 is often considered acceptable. This is based on a 10 x uncertainty factor to account for the possibility that humans are more sensitivity than the te st species to the biochemical/toxicological end point used and an additional 10x factor to acco unt for possible differences in sensitivity within the human population.

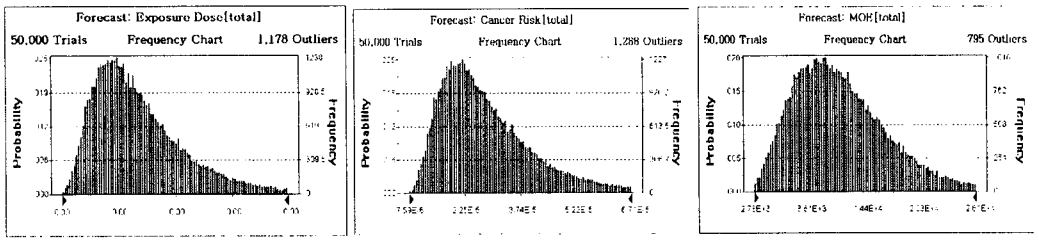

Fig 2. Distribution of Total Exposure Dose, Total Cancer Risk and Total MOE

Reference

1. Chris F. Willinson and James C. Lamb IV. The potential health effets of phthalate esters in children's toys : A review and risk assessment. *Regul. Toxicol. Pharmacol.* 30, 140-155, 19 99
2. John Doull, et al., A cancer risk assessment of di(2-ethylhexyl)phthalate: Application of th e new U.S.EPA risk assessment guidelines. *Regul. Toxicol. Pharmacol.* 29, 327-357, 1999
3. National Toxicological Program(NTP), Carcinogenesis bioassay of di(2-ethylhexyl)phthalate i n F344 rats and B6C3F1 mice(feed study). *Tech. Rep. Ser.* 217
4. U.S.EPA. Proposed guidelines for Carcinogen Risk Assessment. Office of Research and Dev elopment, U.S.EPA. *Fed. Reg.* 61(79). 17690-18011
5. U.S.EPA. Integrated Risk Information System : di(2-ethylhexyl)phthalate, 2000
6. Poland, A. Reflections on risk assessment of receptor-acting xenobiotics. *Regul. Toxicol. Ph armacol.* 26, 41-43, 1997
7. David, R. M., Moore, M.R. Cifone, M.A., Finney, D.C., and Guest, D. Correlation of pero xisome proliferation and oncogenicity of di(2-ethylhexyl)phthalate in mice. *Fundam. Appl. T oxicol.* 36(Suppl.), 173
8. Decisioneering Co., Crystal Ball professional; 2000