European Council for Plasticisers and Intermediates
COMMITTED TO THE SCIENCE OF SAFETY

California State Office of Environmental Hazard Assessment proposal to establish a specific regulatory level posing no significant risk for Diisononyl Phthalate by amending Title 27, California Code of Regulations, section 25705

To Ms. Monet Vela
Office of Environmental Health Hazard Assessment
1001 I Street, 23rd floor
Sacramento, California 95814-4010

Dear Ms. Monet Vela,

On behalf of ECPI, I am pleased to share with you our comments on the proposed NSRL for DINP.

In a corresponding regulatory amendment Cal OEHHA adopted a No Significant Risk Level (NSRL) for Di-isononyl phthalate (DINP) under Proposition 65 in Title 27, California Code of Regulations, section 25705 (b). The proposed NSRL for DINP was derived using methods described in Section 25703 and is based on carcinogenicity studies conducted in rodents. Cal. OEHHA proposed a NSRL of 146 micrograms/day for DINP.

According to Section 25703 (a) the derived NSRL is based on the most sensitive scientific studies deemed to be of sufficient quality. Cal. OEHHA reported in the corresponding amendment that four two-year diet studies conducted in male and female rats (Moore; 1998, Lington et al.; 1997) turned out to meet best the criteria as stated in Section 25703. Both studies have been performed in Fisher 344 rats exposed to DINP in dietary concentrations in a range of 0 – 12.000 ppm (Moore; 1998) and 0 – 6000 ppm (Lington et al.; 1997). Moore (1998, as reviewed in CPSC, 2001) reported statistically significant increase in combined hepatocellular adenoma and carcinoma for both sexes in the highest dose of DINP applied (12.000 ppm) and statistically significant increase in Mononuclear Cell Leukemia (MNCL) for both sexes (≥ 6.000 ppm). Moore reported these effects to be the predominant effects related to treatment of the Fisher 344 rats with DINP. Upon treatment with DINP Lington et al. (1997) reported a statistically significant increase in MNCL for both sexes (≥ 3.000 ppm for male and ≥ 6.000 ppm for female Fisher 344 rats) and a statistically significant increase of liver carcinoma in male Fisher 344 rats (6.000 ppm). However, Lington et al. (1997) concluded from their overall study-results that DINP did not produce treatment-related preneoplastic and neoplastic lesions in the in the liver based on the data presented.

Finally, by taking into account liver effects and MNCL in Fisher 344 rats an overall "Human Cancer Potency" for DINP is derived from the geometric mean of the human cancer potency estimates derived from each of the four studies, yielding a mean potency of 0.0048 $(mg/kg\text{-}d)^{-1}$. Underlying animal cancer slope factors are in a range of 0.000663 (for MNCL; Moore 1998) to 0,00284 (for liver effects and MNCL; Lington et al. 1997)

In the evaluation of new scientific evidence concerning DINP and DIDP (2013) the European ECHA Risk Assessment Committee (RAC) also referred to slight, but significant increase of liver carcinoma observed in male Fisher 344 rats (Exxon; 1986) after high dose exposure levels of DINP (307 mg/kg bw/day) These findings were supported by Aristech in 1994 (733 mg/kg bw/day for males and 885 mg/kg bw/day for females). However it was generally suggested that peroxisome proliferation is the underlying mode of action for development of liver tumors derived from exposure of Fisher 344 rats to DINP. This is well in line with CHAP (2001) and CPSC (2010a) where it was stated that DINP causes cancer in the liver of Fisher 344 rats by a PPARalpha-mediated mechanism that is pronounced in rodents and proposed to be not relevant in the human system. Overall the US CPSC in 2010 did not consider the evidence to be sufficient to consider carcinogenicity as a potential risk derived from exposure of humans to DINP.

The formation of MNCL derived from exposure of Fisher 344 rats to DINP has also been reported in the ECHA report on the evaluation of new scientific evidence concerning DINP and DIDP (2013). In a key study performed by Exxon (1986) MNCL was statistically significant at high dose levels in both sexes. In the Aristech study (1994) MNCL was statistically significant at dose levels ≥ 0.6 % in a two year dietary study also performed in Fisher 344 rats. However it has to be pointed out, that MNCL is a common acute leukemia type disorder that is spontaneously developed by Fisher 344 rats over 18 month age (Lington et al. 1997; Thomas et al. 2007; US CPSC 2010) and the increased incidence of MNCL in the Fisher 344 rat strain to compounds is expected to be a strain specific effect without important relevance to humans. This conclusion is supported by the fact that formation of MNCL was not observed in similar studies performed e.g. on Sprague-Dawley CD rats. While MNCL in the Fisher 344 rat strain incidentally occurred in untreated rats in a range between 32% - 74% in male rats and 14% up to 52 % in female rats (Hanseman et al. 1998 and 2003; Thomas et al. 2007) the corresponding incidence in Sprague-Dawley rats was reported to be 0.6% (Thomas et al. 2007; Frith 1988). It was indicated by Thomas et al. (2007) that the onset of MNCL in Fisher 344 rats is age-dependent and a genetic origin of the disease has been proposed to be most likely. However, other factors are reported that have an impact on the incidence of MNCL. For example the use of oils as vehicles used for administration of test compounds were reported to induce MNCL (Thomas et al. 2007).

With regard to MNCL, Thomas et al. (2007) suggested that a human counterpart to MNCL in rats most likely exists. During the public hearing scheduled by Cal. OEHHA (25th of February 2015) on the proposed regulatory level, Dr. Richard D. Irons pointed out that the MNCL in Fisher 344 rats shares common cells of origin, immunophenotype, as well as certain molecular and clinical features with Human aggressive NK cell leukemia (ANKL) in humans (Jaffe et al. 2001; Ryder et al. 2007; Chan et al. 2008). However, human ANKL is an extremely rare disease involving clonal Epstein-Barr virus (EBV) while MNCL in Fisher 344 rats is a strain-specific genetically-dependent disease with no evidence of a viral etiology. Furthermore Dr. Irons pointed out that taken together these facts, there is no biological basis to support that MNCL in Fisher 344 rats are a relevant and suitable predictive model for human disease associated with exposure to non-genotoxic agents e.g. alkyl-phthalates.

Taken into account those information we would like to express our doubts that the studies that have been taken into account by Cal. OEHHA for derivation of the proposed NSRL of 146 micrograms/day to comply to Section 25703 of Title 27 California Code of Regulations. The corresponding calculated Human Cancer Potency estimates are based on study results also taking into account MNCL as potential lead effect induced in Fisher 344 rats as relevant study endpoint. However, the present comments do strongly support the proposal that data on induction of MNCL derived from Fisher 344 rats do not provide sufficient quality and accuracy and should therefore not been taken into account for the calculation of a Non Significant Risk level of DINP.

Yours sincerely

Dr Stéphane Content, ECPI Manager

About ECPI: The European Council for Plasticisers and Intermediates is a Brussels-based trade association representing the common interests of European manufacturers of plasticisers, alcohols and acids. Member companies are BASF, Deza, Emerald, Evonik, ExxonMobil, Grupa Azoty and Perstorp. ECPI is a sector group of Cefic, the European Chemical Industry Council, which represents the interests of the European chemical industry.

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