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SCIENTIFIC COMMITTEE ON TOXICITY, ECOTOXICITY AND THE ENVIRONMENT (CSTEE)

Opinion on the results of the Risk Assessment of:

1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich and di-"isononyl" phthalate

CAS No.: 68515-48-0
and
CAS No.: 28553-12-0

EINECS No.: 271-090-9
and
EINECS No.: 249-079-5

REPORT VERSION (HUMAN HEALTH EFFECTS): Final report, May 2001

Carried out in the framework of Council Regulation (EEC) 793/93 on the evaluation and control of the risks of existing substances[1]

Opinion expressed at the 27th CSTEE plenary meeting

Brussels, 30 October 2001

[1] Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of those substances if they are produced or imported into the Community in volumes above 10 tonnes per year. The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94, which is supported by a technical guidance document.

Terms of reference

In the context of Regulation 793/93 (Existing Substances Regulation), and on the basis of the examination of the Risk Assessment Report the CSTEE is invited to examine the following issues:

1. Does the CSTEE agree with the conclusions of the Risk Assessment Report?

2. If the CSTEE disagrees with such conclusions, the CSTEE is invited to elaborate on the reasons for this divergence of opinion.

Introduction

There are three different DINPs. DINP 1 (CAS 68515-48-0) is manufactured by the "Polygas" process. DINP 2 (CAS 28553-12-0) is n-butene based. DINP 3 (also CAS 28553-12-0) is n- and iso-butene-based. Consequently, the chemical structures differ, yet they cannot be differentiated on the basis of their physico-chemical properties.

Because of this situation, and the fact that the production of DINP 3 is discontinued, it was concluded by the authors of the report that only one risk assessment report may usefully be presented. However, where possible the proper identification of the three different DINPs was recorded.

DINP is a high volume chemical and is produced by esterification of phthalic anhydride with isononyl alcohol in a closed system. According to the data provided by the producers (ECPI, 1997), the total production volume in the EU was 185,200 t/a as of 1994. As stated in this document, approximately 95% of DINP is used in PVC applications. Of the remaining 5% more than half involves polymer-related uses (rubber) and the remainder is used in non-polymer applications including inks and pigments, adhesives, sealants, paints and lacquers and lubricants. DINP is a general purpose plasticiser with a broad range of applications used in flexible PVC. It is widely used in the toy, construction, and general consumer product markets. It has limited use in food packaging and is not used in medical products.

The range of products that contain DINP is quite broad. Humans may be exposed to DINP by the dermal, inhalation and oral routes. Occupational exposure occurs mainly through inhalation and dermal contact, while consumer exposure occurs mainly through oral and dermal routes. Exposure of children to DINP through children's products has been a public concern.

GENERAL COMMENTS

The health part of the document is of excellent quality. The CSTEE agrees with the general conclusion for most exposure scenarios that there is at present no need for further information and/or testing and for risk reduction measures beyond those that are being applied already. However, the CSTEE disagrees with the use of a NOAEL of 88 mg/kg/d for repeated dose toxicity as used in the RAR. In accordance with the conclusion of a very recent risk assessment report of the US Consumer Products Safety Commission, the CSTEE supports the use of spongiosis hepatis in rats as the critical effect for DINP. Applying a benchmark dose of

12 mg/kg/d for this effect yields a MOS value of 29 for combined consumer exposure of children aged 0.5-3 years warranting conclusion iii).

SPECIFIC COMMENTS

Exposure assessment

DINP vapour pressure is so low that it is difficult to measure, its vapour phase concentrations remain always low, even at temperatures used in some industrial conditions. However, in many circumstances aerosols are formed and become a potentially important source of exposure. Pulmonary uptake may be significant if droplets are in the respirable range, as occurs after recondensation. Pulmonary uptake may also occur when DINP adsorbs to existing respirable airborne particles, as may be the case in the environmental context.

Occupational
DINP is manufactured within a closed system under negative pressure. However, some exposure may occur during the loading and unloading of railroad cars and trucks. Slightly higher exposures may occur during the production of PVC products because of elevated temperatures and more open processes. According to the NTP (2000) report, six studies indicate that exposures are below 1 mg/m^3 during the production of phthalates and below 2 mg/m^3 during the production of PVC. The main source of inhalation exposure originates from aerosol formation.

Occupational exposure may occur by skin contact with pure DINP, or mixtures or end products containing it, and by inhalation. Although it has a very marked lipophilicity, due to its high molecular weight, DINP may be inferred to have a low skin penetration. Oral exposure is not considered to be a significant route of exposure under normal working practices.

Consumers
As DINP is not chemically bound to PVC, it can be released during the entire cycle of life of the end products that are used by consumers, either by use of the end products or via food and food-related products.

Human internal exposures were calculated taking into account the following bioavailability factors as well as differences in oral and inhalation uptake between children and adults: Oral bioavailability: 50% for adults, 100% for new-borns. Inhalation bioavailability: 75% for adults and 100% for new-borns.

DINP is the major replacement product of DEHP in PVC toys and baby equipment. Two routes of exposure are mainly of concern with those of PVC toys: the dermal route during the handling of toys and the oral route during their sucking, chewing and biting.

Indirect: An estimation of the indirect exposure of humans via the environment is 0.001 mg/kg bw/d. Based on the regional concentrations, the total daily intake for infants is 0.0065 mg/kg bw/d.

Combined exposure: Combined exposure (occupational, consumer and via the environment) of different populations may occur. The worst cases combined exposure is estimated to be: Adults: 1.12 mg/kg bw/d; Children (3-15 years old) 0.02 mg/kg bw/d; infants (0.5-3 years of age) 0.41.

Effects assessment

Bioavailability

There are no data available on the oral absorption of DINP in humans. Adult rats excrete approximately 50 per cent of an oral dose of DINP in the urine, the remainder appearing in the faeces but biliary excretion has not been quantitated. Bioavailability of DINP in young animals has not been studied. An adjustment factor of 2 has been used in the RAR for bioavailability of DINP in children 0.5-3 years of age using information from a study with DEHP in rats (Sjöberg et al., 1985). These authors reported a significantly higher AUC, but not C_{max}, for MEHP in 25-day old animals compared to 40- and 60-day old animals. However, this experiment was performed at a very high dose of DEHP (1000 mg/kg/d), a dose at which DEHP hydrolysis appears to become saturated in rats. Thus, it is difficult to support the use of the bioavailability adjustment factor of 2 based on the Sjöberg et al. (1985) study.

Acute toxicity

DINP has a low oral, dermal and inhalation toxicity. Therefore, no classification is indicated according to the EU criteria for acute toxicity.

Irritation

On the whole, DINP may be considered as a very slight skin and eye irritant, with effects reversible in short time (by 24 and 48 hours, the eye irritation completely subsided in all tested rabbit eyes). Thus, no classification is indicated according to the EU criteria for those different end points.

Sensitising properties

These have not been demonstrated with any of the phthalates. However, one out of two Buehler tests with DINP gave a weak positive response. On the other hand, a patch test in humans gave a negative response. The CSTEE agrees with the RAR that overall, a classification of sensitisation properties is not justified with DINP.

Repeated dose toxicity

A number of repeated dose toxicity studies using rats, mice, rabbits, primates and the dog have been reviewed. In the conclusion for repeated dose toxicity the RAR states the following: "...for effects on the liver and kidneys, a NOAEL of 88 mg/kg/d is determined in rats regarding results found in a chronic/carcinogenic study (Aristech, 1994)". The RAR uses this NOAEL for risk characterisation purposes because liver pathology unrelated to peroxisome proliferation was seen in this study. However, in the Exxon study (Lington et al., 1997) using Fischer 344 rats, there was a dose-related increase in relative organ weights of liver and kidney in both males and females with a clear NOAEL of 15(males)-18(females) mg/kg/d. In addition to the increased liver and kidney weights at the LOAEL of 152(females)-184(males) mg/kg/d, males had increased incidences of spongiosis hepatis and serum levels of alkaline phosphatase and transaminases. Spongiosis hepatis, which is a focal degeneration of parasinusoidal cells, presumably not related to peroxisome proliferation, was also seen in

males in the Aristech study (Moore, 1998). The NOAEL/LOAEL for spongiosis hepatis are the same in the two studies as for the increases in liver and kidney weights. The RAR does not use the NOAEL/LOAELs for *spongiosis hepatis* for risk characterisation.

After the RAR was finalised, the Chronic Hazard Advisory Panel on DINP of the US Consumer Product Safety Commission has reported its risk characterisation using *spongiosis hepatis* as the critical endpoint [CSTEE/2001/12-Add. 3 - Report to the U.S. Consumer Product Safety Commission by the Chronic hazard advisory panel on di(isononyl) phthalate (DINP) – June 2001]. The CPSC have calculated the benchmark dose corresponding to a 5% response for this effect to be 12 mg/kg/d based on the Exxon study and 15 mg/kg/d on the Aristech study. The CSTEE finds the approach applied being scientifically sound and supports the use of the benchmark dose for *spongiosis hepatis* as the starting point of the risk characterisation.

Mutagenicity
DINP has been tested for gene mutations in bacteria and mammalian cells *in vitro,* for unscheduled DNA synthesis in hepatocytes, and for chromosomal aberrations *in vitro* and *in vivo*. DINP has also been studied for cell transforming activity in seven experiments with Balb/c-T3 cells. It was recorded as positive in one experiment, had non-significant doubtful activity in three experiments and was negative in three experiments. The CSTEE supports the conclusion of the RAR which suggests that DINP is not genotoxic *in vivo* or *in vitro.*

Carcinogenicity
In chronic/carcinogenicity studies with DINP, significant increases of liver tumours were seen in rats and mice. However, it was demonstrated that DINP induced hepatic peroxisome proliferation in rodents, but not in monkeys. Further evidence for species differences in the hepatic peroxisome proliferator response is presented by Hasmall et al. (Arch. Toxicol., 73, 451-456, 1999; not included in the RAR). *In vitro*, DINP induced beta-oxidation, DNA-synthesis and suppression of apoptosis in cultured rat hepatocytes, but had no effect on these parameters in cultured human hepatocytes. Thus, the CSTEE agrees with the conclusion of the RAR that the carcinogenic responses in rats and mice have little relevance for humans.

In two studies using Fischer rats there were clear increases in the incidences of mononuclear cell leukaemia, but the RAR argues that these should not be considered as relevant to humans. IARC has categorised MNCL as “an unclassified leukaemia with no known human counterpart” and substances which increase MNCL frequency as “not classifiable as to carcinogenicity in humans” (IARC, 1990). The CSTEE supports this view.

In the Exxon combined chronic toxicity/carcinogenicity study (Lington et al., 1997), malignant tubule cell carcinomas were seen in 2 and 4 males of the high dose and high dose recovery groups, respectively. Non-neoplastic histopathological findings in the male kidneys were consistent with hyaline droplet nephropathy. A retrospective study of these changes identified a dose-dependent increase in the accumulation of α2u-globulin in specific regions of male rat kidneys only (Caldwell et al., 1999). Thus, there are good reasons to regard these kidney tumours to be caused by the species and sex-specific α2u-globulin mechanism which is not relevant for humans.

Reproductive toxicity
The NOAEL/LOAEL for reproductive toxicity have been identified in the report to be as follows: Two generation study in rats (oral) – parents and offspring LOAEL 0.2% (159

mg/kg/d). Developmental toxicity in rats - 500 mg/kg/d for both maternal toxicity and developmental toxicity, and in another study 200 mg/kg/d for skeletal variations and 200 mg/kg/d for maternal toxicity. The CSTEE agrees with the conclusions of the RAR that the effects observed in the available studies do not justify classification for effects on fertility and development according to the EU classification criteria.

Regarding possible endocrine disrupting properties of DINP the report points out that investigations on possible mechanism of endocrine disruption for androgenic function are currently being conducted by investigating *in vitro* androgen receptor binding for a number of phthalates and an adipate including DBP, DEHP, DIDP, DINP, DEHA and DNOP. Furthermore, a recent study by Gray et al. (2000) investigating the effects of several phthalates on neonatal rats indicated that DINP might have anti-androgenic potency. However, the reported changes (occurrence of female-like areolas/nipples in infant males) were slight and was only seen at a very high dose (750 mg/kg from gestational day 14 to postnatal day 3). In this respect DINP was about an order of magnitude less active than DEHP and BBP. There has been a proposal by the US National Toxicology Program that further testing be carried out in this area.

Risk characterisation

Very little human data is available and therefore the assessment of the hazardous properties of DINP is based mainly on animal data.

DINP is significantly absorbed from the gastrointestinal tract (at least 50%) and dermal absorption is very limited (<4% in 7 days), and still lower in humans based on *in vivo* and *in vitro* skin penetration studies with various phthalates like DEHP and DIDP. DINP is not accumulated in tissues and is rapidly eliminated. The target organs for chronic toxicity are the liver and the kidney, the underlying mechanisms for some of these effects have little or no relevance for humans (peroxisome proliferation, α2u-globulin related nephropathy). There is no evidence of genotoxic potential of DINP. Using the traditional reproductive toxicity tests revealed that DINP should not be classified as toxic to reproduction. However, there may be some unanswered questions regarding DINP potential to act as an endocrine disrupter, but the available studies indicate that the potency for anti-androgenic effects is very low.

Workers

The CSTEE agrees with the overall results of the risk assessment report that there is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Consumers

For consumers risk assessments were carried out for 3 age groups: Adults and children 3-15 years old; infants 6 months to 3 years; and new-borns 0-6 months. The RAR has incorporated an additional uncertainty factor for new-borns by assigning 100 percent bioavailability by the oral route in new-borns compared to 50 percent for adults. The lowest calculated MOS values are for new-borns 0-6 months and for infants 6 months to 3 years exposed to DINP from various matrices and by multiple pathways with toys, the value being 440 using the NOAEL from the Aristech study of 88 mg/kg/d. The RAR therefore concludes that there is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already. This is in contrast to the opinion of the CSTEE (26/27 November 1998) which raised some concern based on a MOS value of 75 for DINP, using the

NOAEL of 15 mg/kg/d from the Exxon study. The CSTEE supports the conclusions of the US CPSC risk assessment which uses spongiosis hepatis as the critical endpoint with the lowest benchmark dose for a 5 per cent response at 12 mg/kg/d. With an exposure of infants of 0.25 mg/kg/d, this would result in a MOS value of 48 and thus conclusion iii) is warranted.

Indirect exposure: The RAR has calculated an exposure of 0.16 mg/kg/d for infants 6 months to 3 years. The MOS value for this exposure has in the report been calculated to be 282. However, applying the CSTEE-assigned NOAEL value, the MOS value becomes 238, leading the CSTEE to agree with the conclusion of the risk assessment for man exposed indirectly via the environment that there is at present no need for further information and/or testing.

Combined exposure: For combined exposure of adults with occupational exposure there is at present no need for further information and/or testing. For combined exposures of infants (0.5-3 years) with an exposure of 0.41 mg/kg/d the MOS value becomes 29, leading the CSTEE to support the conclusion iii).