EASTMAN

TOXICITY SUMMARY

For

EASTMAN® 168 Plasticizer

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Enumeration of the data for Eastman 168 Plasticizer

Mammalian toxicity	
Oral LD_{50} (rat)	>5000 mg/kg
Oral LD_{50} (mouse)	>3200 mg/kg
Intravenous (IV) LD_{50} (rat)	2000 mg/kg
Dermal LD_{50} (guinea pig)	>20 ml/kg
Skin Irritation (guinea pig)	Slight
Skin Irritation (rabbit)	None
Skin Irritation (human)	None (0.5% in acetone v/v)
Repeated Skin Irritation (guinea pig)	Slight
Eye Irritation (rabbit)	Slight
Eye Irritation (rabbit)	Mildly
Skin Sensitization (guinea pig)	None
Skin Sensitization (human)	None
Inhalation (10 days)	NOAEL 46.3 mg/m^3 (highest dose level)
Oral study (10 days)	NOAEL 1 %
Oral study (21 days)	NOAEL 1.2 %
Oral study (90 days)	NOAEL 1 %
Oral study (104 weeks)	NOEL for carcinogenicity 12000 ppm highest dose tested (equivalent to 666 mg/kg/day in males and 901 mg/kg/day in females). The NOEL for chronic toxicity in the study was 1500 ppm (equivalent to 79 mg/kg/day in males and 102 mg/kg/day in females).
Reproductive Toxicity (2-generation)	NOAEL 1 % for reproductive toxicity. NOAEL for parental and neonatal toxicity 0.3 % due to reductions in bodyweight.
Developmental Toxicity (rat)	NOAEL 1 % (747 mg/kg) for developmental and 0.6 % (458 mg/kg) for maternal toxicity. No alteration of male rat sexual differentiation during development.
Developmental Toxicity (mouse)	NOAEL 0.7 % (1382 mg/kg) for developmental and NOAEL 0.01% (197 mg/kg) for maternal toxicity. No alteration of male rat sexual differentiation during development.
Developmental Toxicity (Special study on male development)	NOEL >750 mg/kg. (Day 14 to Day 3) No effect on male organ development
Developmental Toxicity (Uterotrophic assay)	NOEL >2,000 mg/kg. No estrogenic activity
Genotoxicity/mutagenicity	Ames: negative Chromosomal aberration (*in vitro*): negative CHO/HGPRT assay: negative
Metabolism (*in vitro* and *in vivo*)	The results from both the *in vitro* and *in vivo* experiments indicate that Eastman 168 Plasticizer is not readily absorbed from the GI tract following oral exposures, and that it is likely completely hydrolyzed to TPA and 2-EH (before and or after absorption).
Percutaneous absorption (*in vitro*)	0.103 $\mu g/cm^2/h$, permeability constant $8.39.10^{-8}$ cm/h, no observed skin damage. A continuous 1-hour exposure of both hands was calculated to lead to an internal dose of 1.06 µg/kg.

Ecotoxicity	
ThOD	2.58 g O_2/g
COD	2.7 g O_2/g
Fathead minnow (96h, LC_{50})	> 984 mg/L (= NOEC)
Rainbow trout(96h, LC_{50})	> 0.28 mg/L (= NOEC) MATC > 0.28 mg/L
Snail (96h, LC_{50})	> 984 mg/L (= NOEC)
Oyster (96h, EC_{50})	> 0.624 mg/L (= NOEC)
Algae (72h, EC_{50})	> 0.86 mg/L
Daphnia (48h, EC_{50})	> 1.40 µg/l (= NOEC)
Daphnia (21-day, EC_{50})	> 0.76 µg/l (= NOEC)
Chironomus riparius Sediment-Water Test (28-day EC_{50}, NOEC)	EC50 > 950 mg/kg NOEC = 180 mg/kg
Biodegradation (28 days)	73 % Readily Biodegradable

Toxicity Summary for Eastman 168 Plasticizer

Description

Synonyms	Dioctyl Terephthalate, Di-(2-ethylhexyl) Terephthalate, DEHT, Bis(2-ethylhexyl) Terephthalate, 1,4-Benzene dicarboxylic acid, 2-ethylhexyl ester
CAS Registry Number	6422-86-2
EINECS Number	229-176-9
Molecular Weight	390.57
Molecular Formula	$C_{24}H_{38}O_4$

Physical Properties

Appearance	Colorless liquid
Odor	Mild
Boiling Point	400°C (752°F)
Freezing Point	-48°C (-54°F)
Log K_{ow}	8.39
Vapor Pressure, 217°C (422.6°F)	1.33 mbar (1 mm Hg)
Vapor Pressure, 25°C (77°F)	5.56. 10^{-10} mbar ($4.18.10^{-10}$ mm Hg)(extrapolated values)
Solubility in water	0.4 ug/L (22.5 °C)

Acute Toxicity Data

Oral LD_{50} (rat)	>5000 mg/kg
Oral LD_{50} (mouse)	>3200 mg/kg
Intravenous (IV) LD_{50} (rat)	2000 mg/kg
Dermal LD_{50} (guinea pig)	>20 ml/kg
Skin Irritation (guinea pig)	Slight
Skin Irritation (rabbit)	None
Skin Irritation (human)	None (0.5% in acetone v/v)
Repeated Skin Irritation (guinea pig)	Slight
Eye Irritation (rabbit)	Slight
Eye Irritation (rabbit)	Mildly
Skin Sensitization (guinea pig)	None
Skin Sensitization (human)	None – A HRIPT study using a Modified Draize Procedure was conducted using a total of 203 volunteers. The induction period consisted of 9 applications over a 3-week period using a solution of 0.5% DEHT (v/v) in acetone. Test article was applied to the subject's backs using a semi-occluded patch for approx. 24 hours. Responses observed during induction consisted of an isolated instance of slight redness. Induction was followed by a two-week rest period. The challenge period consisted of a single

application of test material at a naïve skin site. Responses observed during the challenge consisted of a slight redness in two participants. DEHT was concluded to not be irritating, and did not induce contact sensitization.

Conclusion: These data indicate that Eastman 168 Plasticizer has a low order of acute toxicity, is essentially non-irritating, and is not likely to induce contact sensitization in humans. (Unpublished data, Eastman Chemical Company).

Sub-Acute/Sub-Chronic Toxicity Data

Oral study, 10 days

Male Sprague-Dawley rats (5/dose) were fed diets containing 0, 0.1, or 1.0 % (w/w) DEHT for 10 days (equivalent to 0, 85, or 885 mg/kg/day). The study was conducted under GLP assurances. The test compound did not produce mortality. The body weight gain and food consumption was comparable to the controls for all test animals. All hematology determinations were comparable to the controls. The values for all sera clinical chemistry determinations were determined to be within normal limits. The weights of the liver and kidneys were comparable to control. Gross pathology and microscopic examination of approx. 20 tissues revealed no compound-related changes.

Conclusion: The NOAEL for this study was considered to be 1% (885 mg/kg/day) in feed (Unpublished data, Eastman Chemical Company).

Inhalation study, 10 days

Five male Sprague-Dawley rats were exposed to DEHT at a concentration of 46.3 mg/m^3 for 6 hours/day for 10 workdays over a two-week period (primarily as an aerosol). Control rats were treated similarly. The study was conducted under GLP assurances. No mortality was observed. Hematology and clinical chemistry determinations were comparable between the treated rats and control rats. Gross pathology and microscopic examination revealed no compound-related changes.

Conclusion: The NOEL for this study was 46.3 mg/m^3 (Unpublished data, Eastman Chemical Company).

Oral Study, 21 days

Fischer 344 rats (5/sex/dose) were fed diets containing 0, 0.1, 0.5, 1.0, 1.2, or 2.5 % (approx. 0, 100, 500, 1000, 1250, and 2000 mg/kg/day) DEHT for 21 days. Both sexes in the 2.5% group exhibited significant decreases in feed consumption and an associated decrease in weight gains and terminal body weight. These animals also exhibited various clinical signs of sickness. After 21 days animals consuming 1.2% or less DEHT demonstrated body weights similar to controls. No biologically significant alterations in absolute liver weight occurred. In males there was no effect on the absolute weight of the liver (relative weight was increased at 2.5%), while significant decreases were seen in the absolute weights of the kidney at 1.0% and 2.5% (a relative increase was seen at 2.5%), and the testis at 2.5% (a relative increase occurred at the 1.2 and 2.5% levels). The absolute liver weight in females was significantly increased only at the 1.2% dose while the relative to body weight was increased at 1.0, 1.2, and 2.5%. The absolute

kidney weight was also significantly decreased in females at 2.5% (relative weight was increased). Increases seen in relative organ weights at the 2.5% were attributed to the severe decreases in terminal body weight. At the 2.5% level, serum triglycerides were significantly decreased in males and increased in females. Females also showed a significant increase in cholesterol at 2.5% but a significant decrease occurred at the 1.0% level. Electron microscopic examination indicated some evidence of peroxisomal proliferation at 2.5%. Also seen in animals fed 2.5% DEHT were significant increases in some hepatic enzyme activities associated with peroxisome proliferation or induction (a slight, yet significant, increase in one enzyme was seen in males only at 1.2%). The interpretation of this effect at 2.5% is confounded by the results of studies showing that feed intake restriction alone could double peroxisomal oxidizing activity (Ishii, *et al.* (1980). There was no reduction in feed consumption or evidence of peroxisome induction in the livers isolated from animals on the 1.2% DEHT.

Conclusion: The NOAEL in this study was 1.2% (approx. 1250 mg/kg). DEHP, present in the diet at level of 1.2%, was used as a positive control to assess induction of hepatic peroxisomes (Topping *et al.*, 1987).

Oral study, 90 days

Groups of 20 male and female Sprague-Dawley rats were given 0, 0.1, 0.5, or 1.0 % (w/w) DEHT in the diet for 90 days (approximately 0, 54, 277, and 561 mg/kg/day for males and 0, 61, 309, and 617 mg/kg/day for females). No major organ or systemic toxicity resulted from consumption of DEHT in the diet at any exposure level. Occasional changes were noted in some blood parameters (primarily at the 1% dose). Although the effects were statistically significant, they were not always seen in both sexes and their magnitude was of no biological significance. No compounded-related changes were seen in the serum clinical chemistries. Slight increases (a maximum of 11.2%) in relative liver weight were seen at the 1% dose (This effect on relative liver weight was not significant when expressed as a function of brain weight). No adverse effects were observed in the testes of male animals at any dose level. Microscopic examination did not reveal any treatment-related abnormalities in any tissue. Additionally, there appeared to be no evidence of peroxisome proliferation in animals fed 1% DEHT for 90 days based upon a morphometric analyses procedure. The NOAEL in this study was 1.0% in the diet (approximately 561 and 617 mg/kg/day in males and females, respectively) (Barber and Topping 1995).

Conclusion: Repeated exposure of laboratory animals to high levels of Eastman 168 Plasticizer resulted in no overt or organ-specific toxicity in 90-day feeding studies at doses as high as 1.0% (approximately 561-617 mg/kg/day) over 90-days. In addition, it does not appear to induce the proliferation of hepatic peroxisomes following a 90-day dietary exposure of 1.0%. In a 21-day study, no peroxisome proliferation was noted in rats consuming diets containing 1.2% DEHT whereas rodents on a 1.2% DEHP diet did exhibit evidence of induction. Exposure to DEHT does not appear to trigger the biochemical and cellular changes in the liver that are common for *o*-phthalate esters such as DEHP.

Developmental and Reproductive Toxicity Studies

Oral 2-generation reproductive study

This study followed OECD guideline 416. Groups of 30 male and 30 female Sprague-Dawley rats were given 0, 0.3, 0.6, or 1.0% (w/w) DEHT in the diet [approximately 0,150-200, 300-400, 500-700 mg/kg/day for males and 0, 250-300, 500-600, 800-1000 mg/kg/day for females]. The

F_0 animals received the diets for at least 70 days prior to mating and until termination of the generation; the F_1 generation (offspring from the pairing of the F_0 animals; 30 pups/sex/group) received diets following weaning (beginning on PND 22) and for at least 70 days prior to mating. Unselected F_1 pup and all F_2 weanlings were euthanized on PND 21. Sperm evaluations were performed on F_0 and F_1 males from all groups. Uteri and vaginas from all F_0 and F_1 females from the control and high-dose group (as well as any uterus from any group weighing more than 1 gram) were examined by histopathology. All females were allowed to deliver and rear their pups to weaning (lactation day 21). Indicators of physical and functional development were evaluated for the F_1 generation. Reproductive parameters (fertility, mating, days between pairing and coitus, gestation, parturition, and estrous cycling) were unaffected by test article at any dose level during the F_0 and F_1 generations. Mean body weight gains were reduced for F_0 and F_1 males in the 1.0% group at various times as well as in the F_1 0.6% group during the first week following weaning and again beginning Week 23. Mean maternal body weights were reduced in the 1% DEHT group throughout gestation and lactation (Days 1-21), and throughout the F_1 generation. Weight reductions at the 1% exposure level were often associated with slight reductions in food consumption. Three F_0 and seven F_1 females in the 1.0% group were found dead or near death following weaning of their pups. Deaths were not correlated to any histopathologic change in any tissue. No test-article related deaths were observed in the F_0 or F_1 females at the mid- and low-dose levels or in F_0 or F_1 males at any exposure level. Statistical increases and decreases were noted in some organ weights, primarily at the 1.0% exposure level. However, they were often isolated to a single sex, associated with decreased body weight (relative increases) or were not observed consistently in both the F_1 and F_2 offspring. In addition, they were not associated with any macro- or microscopic histological changes. F_1 and F_2 mean live liter sizes, numbers of pups born, percentages of males per litter at birth and postnatal survival were unaffected by parental treatment at all concentrations. Mean F_1 and F_2 offspring weights and weight gains in the mid and high dose were reduced throughout the pre-weaning period. The NOAEL for reproductive toxicity was concluded to be 1.0% in the diet. The NOAEL for parental toxicity and neonatal toxicity was considered to be 0.3% due to reductions in body weights (Faber, *et al.* 2007a).

Oral developmental toxicity - Study 1

This study followed OECD guideline 414. Groups of 25 pregnant Sprague-Dawley rats were treated with 0, 0.3, 0.6, or 1.0 % (w/w) DEHT in the diet beginning on Day 0 of gestation until Day 20 (approximately 0, 226, 458, 747 mg/kg/day). On Day 20, all animals were euthanized, and the uterus and contents excised by caesarean section. The uterus and contents were weighed, and the fetuses removed from the amniotic sacs were weighed and given detailed examinations for external and internal abnormalities. The position and number of fetuses were recorded. The number of viable and non-viable fetuses, resorptions, and implantation sites were also recorded. There was no evidence of embryotoxicity, fetotoxicity, and no effect of treatment on the number of viable fetuses. No visceral or skeletal anomalies were attributed to treatment. Changes in maternal body weights were seen in the highest exposure level and the NOAEL for maternal toxicity was 0.6% (458 mg/kg). The NOAEL for developmental toxicity was 1.0% (747 mg/kg) (Faber, *et al.* 2007b).

Oral developmental toxicity - Study 2

Groups of 10 (control) and 8 (DEHT) pregnant female Sprague-Dawley rats were given 0 or 750 mg/kg/day in 2.5 µl of corn/oil/g body weight DEHT by gavage from gestation day 14 until postnatal day 3. The dose administered included daily adjustments based on individual maternal weight changes throughout the dosing period. No significant maternal toxicity or reduction in

litter sizes was observed. No changes in anogenital distance, testes weight, testes descent, testes lesions, presence of areolas/nipples or vaginal pouch, reproductive organ weights, reproductive organ malformations, or mating behavior of male offspring was observed in the treated animals. DEHP was assessed in this same study and yielded adverse effects at this dose. It was concluded that DEHT did not alter male rat sexual differentiation during development but DEHP does (Gray *et al.*, 2000).

Oral developmental toxicity - Study 3

This study followed OECD guideline 414. Groups of 25 pregnant CD-1 mice were treated with 0, 0.1, 0.3 or 0.7 % (w/w) DEHT in the diet from Day 0 to 18 of gestation. The approximate dose levels received were (0, 197, 592, and 1,382 mg/kg/day). On Day 18, all animals were euthanized, and the uterus and contents excised by caesarean section. The uterus and contents were weighed, and the fetuses removed from the amniotic sacs were weighed and given detailed examinations for external and internal abnormalities. The position and number of fetuses were recorded. The number of viable and non-viable fetuses, resorptions, and implantation sites were also recorded. There was no evidence of embryotoxicity, fetotoxicity, and no effect of treatment on the number of viable fetuses. No visceral or skeletal anomalies were attributed to treatment. Changes in maternal liver weights were seen in the mid and high exposure level animals and the NOEL for maternal toxicity was 0.1% (197 mg/kg). The NOEL for developmental toxicity was 0.7% (1,382 mg/kg) (Faber, *et al.* 2007b).

Oral estrogenicity study (Uterotrophic assay)

Groups of 10 immature female Sprague-Dawley rats were given DEHT orally by gavage once daily on PND 19-21 at a dose rate of 20, 200, 2000 mg/kg/day. Animals were euthanized approximately 24 hours later and had their uterus removed. A reduction in mean body weight gain was observed at the highest dose level. However, no effects were noted on uterine weight or calculated fluid content at any dose. The positive control group given ethinyl-estradiol showed a 3-4 fold increase in uterine weight. It was concluded that DEHT does not possesses estrogenic activity (Faber, *et al.* 2007b).

Conclusion: Results of several robust studies following established guidelines to assess both reproductive and developmental toxicity potential have been conducted on Eastman 168 Plasticizer. The results of these studies indicate there is no evidence of such toxicities when tested in the diet at very high levels 1.0% (rats) and 0.7% (mice). Experimental studies have been conducted to evaluate the potential of DEHT to alter normal postnatal development in males and act as an estrogen agonist in females (uterotrophic assay). DEHT had no "endocrine"-like effects in either study.

Genotoxicity/Mutagenicity Data

Salmonella typhimurium assay (Ames test)	negative (+/- activation by rat liver S9)
Chromosomal aberration assay (*in vitro*)	negative (+/- activation)
CHO/HGPRT assay	negative (+/- activation)

Conclusion: Eastman 168 Plasticizer showed no evidence of genotoxicity in assays assessing for both mutations and chromosomal aberrations. These studies also evaluated mono-ethylhexyl-terephthalate (MEHT) with all results being similar to that of the di-ester (Barber, 1994; DiVincenzo *et al.* 1985).

Metabolism Data

In vitro study: The metabolic hydrolysis rate of DEHT, determined by the formation of free 2-ethylhexanol (2-EH), was studied using a rat intestinal homogenate. The half-life for the disappearance of the di-ester parent molecule was 53.3 minutes. Importantly, the stoichiometry of the reaction at termination showed that 1.97 moles of 2-EH were formed per mole of DEHT indicating a complete hydrolysis to terephthalic acid (TPA). This contrast with DEHP (studied simultaneously) in which the half-life for its disappearance was 12.6 minutes, and there were only 1.2 moles of 2-EH generated per mole of DEHP indicating it forms a stable monoester (MEHP) (Barber *et al.*, 1994).

Oral study: The absorption and metabolism of DEHT were studied by administering [Hexyl-2-^{14}C]DEHT in corn oil by oral gavage at a dose level of 100 mg/kg to 10 adult male Sprague-Dawley rats. Urine, feces and expired air were collected daily for 144 hours and analyzed for the presence of radioactivity and metabolites.

At study termination 93% of the total administered radioactivity was recovered. Most of the recovered radioactivity was found in the feces (56.5%) and urine (31.9%), while 3.6% was isolated in expired air as $^{14}CO_2$, and 1.4% remained with the carcass. Urinary and fecal recovery rates peaked by 10 hours with >95% of the total excreted amount recovered within 24 hours (>99% by 48 hours). The mean amount of non-metabolized [^{14}C]-DEHT recovered in the feces was 36.6% and the percentage of the total DEHT dose recovered in the urine, as unlabelled TPA, was 50.5%. In total 91.7% of the dose can be accounted for as either unchanged DEHT in feces, unlabelled TPA in urine, or as $^{14}CO_2$ in expired air. This balance sheet thus limits the amount of mono(2-ethylhexyl)terephthalate (MEHT) and its metabolites to a maximum of only 9.3% of the orally administered dose (Barber *et al.*, 1994).

Conclusion: The results from both the *in vitro* and *in vivo* experiments indicate that Eastman 168 Plasticizer is not readily absorbed from the GI tract following oral exposures, and that it is likely completely hydrolyzed to TPA and 2-EH (before and or after absorption). Only very minor amounts of MEHT were isolated. This contrasts the metabolic profile of DEHP, an *ortho*-phthalate, which primarily undergoes a partial cleavage to form a stable monoester that is the purported active.

Percutaneous Absorption Data

The rate of percutaneous absorption of [carboxyl-^{14}C]bis(2-ethylhexyl)-1,4-benzenedi-carboxylate (DEHT) through dermatomed sections of human skin was measured *in vitro* (Guerin and Taylor, 2002). An excess of the test substance was applied to sections of human skin contained in glass diffusion cells. Solubility of the test substance in receptor solution was determined not to be a rate-limiting step in skin absorption. The total recovery of the test substance was measured by determining the percentage ^{14}C-labeled test substance remaining in test system components for each test substance cell. The total mean (± SD) ^{14}C-labeled test substance recovery was 104% ± 6%. The majority of ^{14}C was recovered from the donor cell and only 0.056% ± 0.032% was associated with the skin. The measured absorption rate (mean ± SD) was 0.103 ± 0.052 µg/cm^2/hr, and the permeability constant was (8.39 ± 2.17) x 10^{-8} cm/hr. The integrity of each skin specimen was determined by measuring its permeability to tritiated water (^3H_2O) in Phase 1. The mean (± SD) ^3H_2O absorption rate for all skin specimens was 2.04 ± 0.95 mg/cm^2/hr, in agreement with historical and published values. The mean damage ratio, calculated from the rates of ^3H_2O before and after exposure of the skin to the test substance, was similar to the negative control (unexposed) values, indicating that exposure to the test substance for 29 hrs did not significantly damage human skin.

Conclusion: Applying the criteria of Marzulli, Brown, and Maibach (1969), DEHT absorption through human skin is classified as "extremely slow". These data allow the estimation of uptake in man following dermal exposure to the test substance, assuming that the skin absorption rate in man is similar to that observed in this *in vitro* study. For example, if excess test substance were to be in contact with an area of skin equivalent to both hands (approximately 720 cm^2, 70-kg human) continuously for 1 hr, then the calculated internal dose would be 1.06 µg/kg.

Carcinogenic Potential

The carcinogenic potential of Eastman 168 Plasticizer to F-344 rats by dietary administration was assessed over a period of 104 weeks (Eastman Chemical Company, 2005). Four groups of 50 male and 50 female rats received the test material at concentrations of 0, 1500, 6000 or 12000 ppm via the diet. Overall achieved dosages were 79, 324 and 666 mg/kg/day for males and 102, 418 and 901 mg/kg/day for females, respectively. There were no clinical signs of toxicity related to treatment. Bodyweight gain was statistically significantly low throughout the treatment for males and females receiving 12000 ppm (overall bodyweight gain was 93 and 75% of the Control value, respectively). The bodyweight gain of males and females receiving 6000 ppm was also statistically significantly low during the first year of the study (bodyweight gain to Week 52 was 97 and 95% of Control value, respectively). At the end of the study the overall bodyweight gain of these animals was similar to that of the Controls. Food consumption was not affected by treatment. Food conversion efficiency was slightly low during the first 16 weeks of treatment in animals receiving 12000 ppm. The ophthalmic examination in Week 104 indicated an increased incidence of fundic hyperreflection and conjunctival discharge in females receiving 12000 ppm and of anterior capsular opacity in the lens of females receiving 6000 or 12000 ppm. Hematological changes in Week 104 comprised: slightly low hematocrit and hemoglobin concentration in females receiving 12000 ppm; low mean cell hemoglobin and mean cell volume in animals receiving 6000 or 12000 ppm; high erythrocyte count in males receiving 6000 or 12000 ppm. Plasma urea concentrations were high and total cholesterol and triglyceride concentrations were low in Week 104 in females receiving 12000 ppm. Plasma glucose concentrations were slightly high in females receiving 6000 ppm and in animals receiving 12000 ppm. Urinary volume was low and specific gravity was high in Week 103 in males receiving 6000 ppm and in animals receiving 12000 ppm. Urinary protein was reduced in females receiving 12000 ppm and urinary pH was low in animals receiving 6000 or 12000 ppm. The urine of females receiving 6000 ppm and of animals receiving 12000 ppm appeared less cloudy that than of the Controls. Females receiving 12000 ppm had high bodyweight-relative liver and kidney weights after 104 weeks of treatment. Females given 12000 ppm had an increased incidence of dark kidneys and opaque eyes whilst those receiving 6000 or 12000 ppm had a low incidence of pale areas on the liver. There were no treatment-related macroscopic findings in males. There was no effect of treatment upon tumor profile. Non-neoplastic changes related to treatment were present in the kidneys, liver, eyes and nasal turbinates. In the kidneys a decreased incidence of chronic progressive nephropathy was seen in females at 6000 or 12000 ppm and a decreased incidence of mineralization of the pelvic/papillary epithelium was seen in males and females at 6000 or 12000 ppm and in males at 1500 ppm. In the liver a decreased incidence of periportal hepatocyte vacuolation was seen in all treated males. In the eyes, there was an increased in the severity (using a morphological based scoring index of 0-1) of the loss of the outer nuclear layer of the retina of females at 6000 and 12000 ppm. In the nasal turbinates, an increased incidence of prominent eosinophilic inclusions was seen in females at 6000 or 12000 ppm. The significance of this nasal change was deemed to no be toxicologically relevant.

Conclusion: It is concluded that the oral administration of Eastman 168 Plasticizer via the diet to F-344 rats for 104 weeks at concentrations of up to 12000 ppm was well-tolerated. There was no effect upon tumor incidence and, therefore, the no-observed-effect level (NOEL) for tumorogenicity is at least 12000 ppm (equivalent to 666 mg/kg/day in males and 901 mg/kg/day in females). Toxic responses were confined to low weight gain and food conversion efficiency in males and females receiving 6000 or 12000 ppm and ocular changes in females receiving 6000 or 12000 ppm. Consequently the no-observed-effect level (NOEL) for chronic toxicity in the study was 1500 ppm (equivalent to 79 mg/kg/day in males and 102 mg/kg/day in females) (Deyo, J. A., 2008).

ENVIRONMENTAL TOXICITY

Oxygen Demand Data:

ThOD 2.58 g oxygen/g
COD 2.7 g oxygen/g

Definitions: NOEC = No-Observed-Effect Concentration
NAEC = No-Adverse-Effect Concentration
MATC = Maximum Acceptable Toxicant Concentration
LC50 = Lethal Concentration to 50% of the test organisms
EC50 = Effective Concentration causing a 50% reduction in the test endpoint

Acute Aquatic Effects Data:

Daphnia magna	48-h EC_{50} >1.4 ug/L[a]
Fathead minnow	96-h LC_{50} >984 mg/L[b], 96-h survival NOEC ≥984 mg/L[b]
Snail	96-h LC_{50} >984 mg/L[b], 96-h survival NOEC ≥984 mg/L[b]
Rainbow trout:	96-h LC_{50} >0.28 mg/L[c], 7-day survival NOEC ≥0.28 mg/L[c]
Oyster	96-h EC_{50} >0.624 mg/L[d] (shell deposition), survival NOEC ≥0.624 mg/L[d]
Algae	72-h EC_{50} >0.86 mg/L[e]

a.) A static, 48-hour immobilization test was conducted using Daphnia magna. No adverse effects were seen. The study followed OECD Guideline 202 and GLP assurances.

b.) A static, 96-hour toxicity test was conducted using fathead minnows (*Pimephales promelas*) and planorbid snails (*Helisoma trivolvis*) and two nominal concentrations (100 µl/L and 1000 µl/L). No effects were observed at the highest concentration (orders of magnitude above solubility under test conditions).

c.) A 7-day, flow-through toxicity test was conducted under GLP assurances with rainbow trout (*Salmo gairdneri*) using five concentrations, with the maximum concentration at the limit of solubility under test conditions (0.35 mg/L nominal, 0.28 mg/L measured mean). No mortality was observed in any concentration through 7-days.

d.) A 96-hour, flow-through oyster shell deposition test was conducted using eastern oysters (*Crassostrea virginica*) and five concentrations conducted under GLP assurances. Mo mortality or reduction in shell deposition was observed in any concentration up to the maximum mean (measured) concentration of 624 µg/L (limit of solubility in sea water).

e.) A 72-hour growth inhibition limit test using the alga *Selenastrum capricornutum* was conducted using a nominal concentration and conducted under GLP assurances. Two measures of growth (biomass E_bC_{50}, and growth rate E_rC_{50}) were not adversely impacted at 0.86 mg/L, the mean concentration measured during the test (limit of solubility under test conditions).

Chronic/Sub-Chronic Aquatic Effects Data

Daphnia magna:	21-day EC50 >0.76 μg/L, 21-day NOEC = 0.76 μg/L
Rainbow trout:	MATC >0.28 mg/L
Chironomus riparius	28-day EC50 > 950 mg/kg (development & emergence), 28-day NOEC (emergence) = 180 mg/kg

Daphnia magna

A 21-day full life cycle toxicity test using *Daphnia magna* under flow-through conditions was conducted using a high nominal concentration of 1.0 μg/l with a dilutor system providing four additional 50% dilution concentrations (0.50, 0.25, 0.13, and 0.063 μg/l). A control and solvent control were also included in the test. The test solutions for each treatment level were measured on days 0, 7, 14, and 21 providing mean measured test concentrations of 0.039, 0.084, 0.17, 0.35, and 0.76 μg active ingredient/l. The biological effects monitored were survival/immobility, reproduction, organism length and dry weight. No biologically relevant statistical differences were detected between the controls and treatments.

Rainbow trout

A flow-through 60-day post-hatch early life stage toxicity study of DEHT to rainbow trout was conducted to estimate the MATC limits. Hatchability of rainbow trout eggs after 11 days of continuous exposure to 0.014, 0.024, 0.047, 0.15, and 0.28 mg/L was not significantly affected when compared to control. Likewise, survival of fry between hatch and 60 days of exposure to all test concentrations was not significantly reduced. Growth of trout fry, as measured by wet weight after 60 days of exposure to all test concentrations, was not significantly reduced. Based on these data, the MATC was determined to be >0.28 mg/L (measured). This was the highest concentration tested due to limits of water solubility.

Chironomus riparius

A Sediment-Water Chironomid Toxicity Test using Spiked Sediment (OECD Method 218) was conducted with DEHT using five concentrations ranging from 92.1-950 mg/kg. The endpoint of the test was the number of live, emerged adult midges. The results indicated that the 28-day EC_{50} (reduction in emergence) was greater than 950 mg/kg. The 28-day EC_{50} (development rate) was also greater than 950 mg/kg. There were no significant differences between the numbers of males and females that emerged. A subset of replicates was sacrificed to determine the 10-day larval survival and growth data. There were no statistical differences in growth (weight) between the control and any of the test groups at 10 days. There were statistical differences in survival between the control and some of the test groups, but the number of larvae surviving on day 10 was similar to the number observed emerging to adult flies on day 28. The No Observable Effect Concentration (NOEC) for emergence was 180 mg/kg.

Conclusions: The solubility of this material in water is very low. In distilled water the solubility has been reported to be 0.4 μg/l. The aquatic toxicity data indicates that there were no acute or chronic effects for any species tested at concentrations at or near the water solubility limit of the material. One study also indicated no impact on survival at concentrations that were orders of magnitude above the solubility limit for the test conditions. Sub-lethal effects such as growth (*D. magna*, algae, trout), reproduction (*D. magna*), shell deposition (oyster), and egg hatchability (trout) were also not adversely impacted in any of the studies at the concentrations tested. Because DEHT would have a strong tendency to sorb to sediments in the aquatic environment,

an OECD sediment-water chironomid toxicity test using spiked sediments was conducted to demonstrate that DEHT would not have cause adverse impacts to aquatic sediment dwelling organisms. The sediment test indicated that the EC50 was greater than the highest test concentration recommended by the method.

Biodegradation Data

A 28-day OECD 301B Ready Biodegradation study was conducted on Eastman 168 Plasticizer. This study is based upon measured CO^2 evolution as the material undergoes ultimate degradation by microorganisms to CO^2 and water. 168 Plasticizer exhibited 73.05% biodegradation over 28 days and met the criteria for ready biodegradation by achieving > 60% degradation during a 10 day window after 10% degradation was achieved.

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