XYLENE

This is a compilation of abstracts of articles identified during the preliminary toxicological evaluation of evidence on the developmental and reproductive toxicity of xylene (xylol, a mixture of o-, m-, and p- xylene; for the mixture: CAS# 1330-20-7). Xylene is most commonly used as a solvent or as feedstock in polymer production.

The abstracts compiled below are from animal toxicity and epidemiologic studies reporting on developmental and reproductive sequelae related to exposure to xylene, as well as other relevant investigations (e.g., *in vitro* studies or studies in non-mammalian animal species). This information was used to screen chemicals to propose for listing consideration by the Developmental and Reproductive Toxicant Identification Committee. The criteria for passing the current screen are the existence of the following number of reports of an increase in adverse developmental or reproductive toxicity outcomes in mammalian species:

1) a total of 15 or more reports across all of the endpoints (developmental toxicity,female reproductive toxicity, male reproductive toxicity); or
2) 10 or more reports for any one category of the following three categories: developmental toxicity, female reproductive toxicity, or male reproductive toxicity.

There were a total of 146 studies identified in the literature search on xylene (some studies may have reported more than one adverse effect). The table below shows how xylene passes the screen.

Endpoints	Reports of adverse effects		Reports of no adverse effects	
	Animal	Human	Animal	Human
Developmental	10	1	1	0
Female reproductive	1	2	0	0
Male reproductive	2	1	0	0
Total	13	4	1	0

In addition to the reports enumerated in the table, the search identified:

- 26 other related studies or meeting presentations (titles of reports only provided below)
- 16 publications with a relevant title but no abstract.

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I. Animal Developmental and Reproductive Toxicity Studies

A. Studies reporting developmental or reproductive toxicity

i. Developmental toxicity

a. Studies identified in the open literature search

Developmental toxicities of ethylbenzene, ortho-, meta-, para-xylene and technical xylene in rats following inhalation exposure.
Saillenfait A. M., Gallissot F., Morel G. and Bonnet P.
Food Chem Toxicol. 2003;41(3):415-29.

The developmental toxicities of ethylbenzene, o-, m-, p-xylene and technical xylene were studied in Sprague-Dawley rats after inhalation exposure. Animals were exposed to either of these agents at 100, 500, 1000 or 2000 ppm, for 6 h/day, during days 6-20 of gestation. All the agents tested caused maternal toxicity expressed as a reduction in maternal body weight gain at 1000 and 2000 ppm. Decreased corrected weight gain and food consumption were observed at 1000 and 2000 ppm ethylbenzene, o-, m- or p-xylene, and at 2000 ppm technical xylene. No evidence of teratogenic effects was found after exposure to any of these agents up to 2000 ppm. Fetal toxicity evidenced by significant decreases in fetal body weights occurred at concentrations of 500 ppm or greater of o-xylene or technical xylene, and 1000 ppm or greater of ethylbenzene, m- or p-xylene. A significant increase in the mean percentage of fetuses per litter with skeletal variations was also noted at 2000 ppm ethylbenzene, o- and p-xylene. In summary, all tested agents produced developmental toxicity at 1000 and 2000 ppm, concentrations that also produced significant maternal toxicity. With o-xylene and technical xylene, developmental toxicity also occurred at 500 ppm, in the absence of maternal toxic effects. However, the only indication of a treatment-related effect was a slight decrease in fetal weight.

Developmental toxicity of inhaled ortho-, meta-, and para-xylene in rats.
Saillenfait A. M., Gallissot F. and Morel G.
Reprod Toxicol. 2002;16(4):417.

Xylene, a solvent with wide industrial applications, exists in three isomeric forms: ortho, meta, and para. This study was undertaken to evaluate the developmental toxicity of the three xylene isomers in rats following inhalation exposure throughout the embryonic and fetal periods. Each of the chemicals was tested in a separate experiment following the same general protocol. Pregnant Sprague-Dawley rats were exposed, whole body, to 0, 100, 500, 1000 or 2000 ppm ortho-, meta-, or para-xylene, by inhalation, for 6 h/day, from Gestational Days (GD) 6 through 20. Maternal food consumption, body weights and clinical signs were monitored at regular intervals throughout gestation. At termination (GD 21), maternal animals (20-26 per group) were evaluated for gestational

outcome. Live fetuses were weighed and submitted to external examination. Half of the fetuses were evaluated for visceral defects and the other half for skeletal defects. No maternal death was observed. Body weight gain, absolute weight gain, and food consumption of the dams were significantly decreased at 1000 and 2000 ppm ortho-, meta-, and para-xylene. None of the three isomers was teratogenic or embryolethal up to 2000 ppm, which produced overt signs of maternal toxicity. Developmental toxicity was indicated by concentration-related depression of fetal weights. Decreases were statistically significant at greater than or equal to 500 ppm ortho-xylene and at 1000 and 2000 ppm meta- and para-xylene. In addition, the overall incidence of skeletal variations was significantly elevated at 2000 ppm ortho- and para-xylene, and the occurrence of incomplete ossification of thoracic centra (a common skeletal variant in rat fetuses) was increased at 2000 ppm meta-xylene. Thus, the no-observable-adverse-effect level (NOAEL) for maternal toxicity was 500 ppm for the three isomers. The NOAELs for developmental toxicity were 100 ppm for ortho-xylene and 500 ppm for meta- and para-xylene.

The effect of xylene inhalation on the rat liver.
Kükner A, Canpolat L, Ozan E, Gökçimen A, Ozan S, Doğrul M.
Acta Physiol Hung. 1997;85(3):231-41.

In this study, 11,284 mg/m3 (2600 ppm) of xylene was administered for 8 hours a day to pregnant rats by means of inhalation, starting from the sixth day of their pregnancies. Furthermore, while a group of non-pregnant rats inhaled the same amount of xylene during the same period, the control group inhaled clean air. Consequently, in addition to the embryotoxic effects of xylene, the effects on the various tissues of the mothers and their litters were observed light and electron microscopes. No external anomalies were observed in any of the rats born at the end of the 21st day, and there were no macroscopic defects in their organs either. While following xylene inhalation no structural defects in the kidney and pancreas was found, expansions in the smooth endoplasmic reticulum of the liver tissues, increases in the lysosomes, and defective mitochondrion structures were found in the pregnant and non-pregnant rats. It was noticed that xylene in particular caused structural defects in the liver of the fetus. Compared to the control groups, increases were observed in the activities of the AST, ALT, ALP, and Arginase enzymes in the liver.

Long-lasting neurobehavioral effects of prenatal exposure to xylene in rats.
Hass U., Lund S. P. and Simonsen L.
Neurotoxicology. 1997; 18(2):547-51.

The persistence of neurobehavioral effects in female rats (Mol:WIST) exposed to 500 ppm technical xylene (dimethylbenzene, CAS-no 1330-20-7) for 6 hours per day on days 7-20 of prenatal development was studied. The dose level was selected so as not to induce maternal toxicity or decreased viability of offspring. Investigations of learning and memory abilities were performed using a Morris water maze. This task requires rats to spatially navigate, using distal extramaze cues to locate a small platform under the

surface of the water in a large pool. At the age of 16 weeks, the exposed offspring showed impairments when the platform was relocated in the pool. Impaired performances after platform relocation were also observed in exposed offspring at 28 and 55 weeks of age, although the difference was not statistically significant at 55 weeks. These data could indicate that the effect was partly reversible, although over a long time period. However, another explanation could be that the animals became more practised at solving the problem (finding the platform) as continued testing occurred and therefore were able to compensate for the neurotoxic effect of the prenatal xylene exposure. Further studies are planned to investigate whether neurobehavioral effects resulting from prenatal xylene exposure can interact with neurophysiological aging processes.

Long-lasting neurobehavioral effects of prenatal exposure to xylene in rats.
Hass U., Lund S. P. and Simonsen L.
Neurotoxicology. 1995;16(4):761.

The persistence of neurobehavioral effects in female rats (Mol:WIST) after prenatal exposure to 500 ppm technical xylene (dimethylbenzene, CAS-no 1330-20-7) for 6 hours per day on days 7-20 of prenatal development was studied. The dose level was selected as not to induce maternal toxicity or decreased viability of offspring. Investigations of learning and memory abilities were performed in Morris water maze. This task requires rats to spatially navigate, using distal extramaze cues to locate a small platform under the surface of the water in a large pool. At the age of 12-16 weeks, the exposed offspring showed impairments when the platform was relocated to another position in the pool. Impaired performances after platform relocation were observed in exposed offspring also at 28 weeks and at 55 weeks, although the difference declined during the period and was not statistically significant at the age of 55 weeks. This indicates either that the effect was reversible over a very long time period or that the animals became familiar with the Morris water maze test and were able to compensate for the neurotoxic effect of the prenatal xylene exposure. Further studies are planned to investigate whether neurobehavioral effects resulting from prenatal xylene exposure can interact with the consequences of aging.

Effects of prenatal exposure to xylene on postnatal development and behavior in rats. Hass U., Lund S. P., Simonsen L. and Fries A. S.
Neurotoxicol Teratol. 1995 May-Jun; 17(3):341-9.

The effects of prenatal exposure to the organic solvent xylene (dimethylbenzene, CAS-no 1330-20-7) on postnatal development and behavior in rats were studied. Pregnant rats (Mol:WIST) were exposed to 500 ppm technical xylene 6 h per day on gestation days 7-20. The dose level was selected so as not to induce maternal toxicity or decrease the viability of offspring. In the exposed offspring, a delay in the ontogeny of the air righting reflex, a lower absolute brain weight, and impaired performance in behavioral tests for neuromotor abilities (Rotarod) and for learning and memory (Morris water maze) were found. Generally, the effects were most marked in the female

offspring.

Prenatal toxicity of xylene inhalation in the rat: a teratogenicity and postnatal study.
Hass U. and Jakobsen B. M.

Pharmacol Toxicol. 1993;73(1):20-3. Technical xylene (cas. nr. 1330-20-7) was investigated for development toxicity in a teratology and in a postnatal study. Rats (Mol: WIST) were exposed to 500 p.p.m. 6 hr per day on days 4 to 20 of gestation. There were no signs of maternal toxicity. In the teratology study, no exposure-related differences were found except for delayed ossification of os maxillare. In the postnatal study, the xylene-exposed pups had a higher body weight and an impaired performance on a motor ability test (Rotarod). Due to the possibility of direct toxic effects of xylene on the developing central nervous system, further studies are needed to investigate dose-effect relationship for this type of effects.

Behavioral and neurochemical consequences of perinatal exposure to Type I and Type II pyrethroid formulations.
Sylianco-Wu L., Kallman M., Wilson M., Slikker W., Jr., Hikal A., Ali S. and Holson R.
Neurotoxicol Teratol. 1990;12:565.

This investigation explored the behavioral and neurochemical toxicity of perinatal oral exposure to Ambush (Type I) and Pydrin (Type II), two pyrethroid formulations. Thirty-six female rats were mated and exposed to various pyrethroid formulations by oral gavage from the first gestational day until their pups (culled to 8/litter) were 12 days old. Six mothers were exposed daily to one of the following treatments: corn oil control, corn oil+96% xylene, 1.25 mg/kg Pydrin (pesticidal ingredient fenvalerate), 0.125 mg/kg Pydrin, 4.0 mg/kg Ambush (pesticidal ingredient permethrin), or 0.4 mg/kg Ambush. Behavioral evaluations of locomotor activity, muscular coordination and passive avoidance learning were conducted on half of the pups from each litter (N = 24 pups/treatment condition). The other pups were sacrificed, brains were removed and sectioned into frontal cortex, hippocampus, caudate, and cerebellum for neurochemical assessment. The monoamines DA, DOPAC, 5-HIAA, 5-HT and HVA levels were determined and the amino acids aspartate, glutamate, glutamine, glycine, GABA, and taurine were determined for each of the brain regions. Gestational duration was shortened by exposure to the high doses of Pydrin and Ambush but only pups from the 4.0 mg/kg Ambush group were significantly lighter. No physical malformations were observed in pups from any of the treatment conditions, although the high Pydrin exposure condition resulted in a 4% death rate. Behavioral changes were seen for both locomotor activity and muscular coordination. The shape of across-session habituation of locomotion was different for the xylene and corn oil and the high dose Ambush groups. Both groups were less active on day 1 and more active on days 2 and 3 than the other pups. The high doses of Ambush and Pydrin produced slower intrasession habituation. Muscular coordination was improved slightly following low dose exposure to both pesticides and reduced following high dose exposures. Regional brain weights

were normal for the cortex, cerebellum and caudate but the hippocampus was 64% heavier for pups treated with 4.0 mg/kg Ambush. Amino acid determinations indicated that the cerebellum was most affected where glutamate, glutamine, aspartate and taurine were reduced following xylene or pyrethroid exposure. The biogenic amine transmitter 5-HT was reduced in several brain regions following pyrethroid exposures. These data suggest that levels of Ambush and Pydrin as low as the LD50/10,000 can alter behavior and neurotransmitter functioning.

On the embryotoxic effects of benzene and its alkyl derivatives in mice, rats and rabbits.
Ungváry G, Tátrai E
Arch Toxicol Suppl. 1985; 8:425-30.

Groups of CFY rats were exposed to inhalation of ethylbenzene at 600, 1200 or 2400 mg/m3 or xylene at 250, 1900 or 3400 mg/m3 or Aromatol at 500, 1000 or 2000 mg/m3 atmospheric concentration for 24 h/day from day 7 to day 15 of pregnancy, or for 2-4 hours only on the 18th or 20th day of gestation. CFLP mice and NZ rabbits were exposed to inhalation of 500 mg/m3 or 1000 mg/m3 benzene, toluene, ortho-, meta-, para-xylene, ethylbenzene, xylene or Aromatol for 24 h/day from day 6 to day 15 of pregnancy. Untreated animals and groups inhaling pure air served as controls. All components of the xylene and Aromatol crossed the placenta and were present in fetal blood and amniotic fluid, as well. The maternal toxic effects at all solvents were moderate and dose dependent. All solvents (at higher concentrations) brought about skeletal and weight retardation in fetuses of rats and mice. At highest concentration some solvents increased the post-implantation loss in rats and mice. All solvents caused spontaneous abortion in rabbits at 1000 mg/m3 atmospheric concentration. Only ethylbenzene and Aromatol increased the malformation rate in rats and mice. No other solvent applied proved to be teratogenic either in mice, rats or rabbits.

Prenatal toxicity of xylene.
Mirkova E., Zaikov C., Antov G., Mikhailova A., Khinkova L. and Benchev I.
J Hyg Epidemiol Microbiol Immunol. 1983;27(3):337-43.

Prenatal inhalation toxicity of xylene (industrial mixture of isomers) was studied in experiments of white Wistar rats exposed daily (6 hours a day, 5 days in a week) to concentrations of 10, 50 (MAC for xylene in the air of work environment in Bulgaria) and 500 mg.m-3 throughout the period of gestation from the first to the 21st day. Both routine teratological indices and biochemical and physiological methods of observation were used to evaluate the integrity of the individual organs - liver, brain, lungs and myocardium of the generation in the postnatal period of development. In concentrations of 50 and 500 mg.m-3, xylene exhibits pronounced embryotoxic and teratogenic effects. Postimplantation embryonal mortality increases, the process of physical development of the fetus is delayed, the incidence of induced anomalies of internal organs (hydrocephalus, microphthalmia, intracerebral haematomas, haemorrhages in the liver) is enhanced, the processes of ossification of the sternum and the skull are impaired. In

concentrations of 50 and 500 mg.m-3, xylene causes disturbances in postnatal development of F1 generation. The concentration of 50 mg.m-3 is the threshold of the embryotropic effect of the solvent. Measures for the protection of women at work are proposed to reduce industrial hazard of developing antenatal pathology in the newborn of workwomen in xylene works.

ii. Female reproductive toxicity

a. Studies identified in the open literature search

[Evaluation of inhalation toxicity of organic solvent xylene in pregnant rats].
Mirkova E, Antov G, Zaĭkov Kh, Ganchovska V.
Probl Khig. 1982;7:60-7.

The objective of the present experimental study was the assessment of organism susceptibility to the toxic xylene effect during gestation period, with a view to elaborating recommendations for female work protection. The experiments were carried out in a comparative aspect in 60 pregnant and 60 virgin, sexually matured female albino rats, exposed to 1850 and 467.8 mg/m3 technical xylene in inhalation chambers--levels 40 and 10 times higher than MAC of the solvent, in the course of 21 days (period of gestation of rats), 5 hours daily, 5 times a week. The assessment of inhalation toxicity of xylene is based on the data from the complex biochemical investigations in serum, liver, brain, myocardium and aorta, supported by pathomorphological studies. Xylene disturbs the balance of serum lipid fractions with both levels of inhalation effect and has a manifested hepatotoxic and cardiovascular effect to pregnant animals. Less manifested disorders in serum lipid profile, liver and the brain of the female, non-pregnant rats, were established with the administration of high xylene concentrations only, suggesting the higher vulnerability of the pregnant organism to the toxic xylene effect. Recommendations for early labour readjustment of pregnant women engaged in xylene production are presented on the base of the data obtained about the disorders of vital functions of organism during gestation period, supported by epidemiological observations and the presence of experimentally established specific embryotoxic effect of xylene at MAC levels.

iii. Male reproductive toxicity

a. Studies identified in the open literature search

Induction of morphologically abnormal sperm in rats exposed to O-Xylene.
Washington W. J., Murthy R. C., Doye A., Eugene K., Brown D. and Bradley I.
Arch Androl. 1983, Dec; 11(3):233-7.

An analysis of sperm abnormalities can be used as a rapid method to determine the mutagenic potential of chemical agents as well as the toxic potential of chemicals on the

whole animal. O-Xylene was investigated for its potential mutagenicity by the sperm abnormality assay. Sprague Dawley rats 10-16 weeks old were injected intraperitoneally (ip) with 0.5 and 1.5 ml/kg body weight of o-xylene in corn oil. Five weeks after treatment, animals were sacrificed and sperm examined for morphological abnormalities. Several morphologically abnormal sperm types were observed; among these were those with amorphous heads, and banana-like heads. Animals housed at room temperatures of 20-24 degrees C showed no significant increase in abnormal sperm over the control. Rats housed at temperatures between 24 and 30 degrees C after ip injection with 0.5 ml/kg o-xylene showed a significant increase in abnormal sperm.

Influence of lacquer thinner and some organic solvents on reproductive and accessory reproductive organs in the male rat.
Yamada K.
Biol Pharm Bull. 1993;16(4):425-7.

The effects of thinner and its main components, toluene, xylene, methanol, and ethyl acetate, on reproductive and accessory reproductive organs in male rats were studied. The vapour from these organic solvents was inhaled twice a day for 7 d. Following inhalation of thinner vapour for 7 d, the weights of the testes and prostate fell and acid phosphatase activity in the prostate and plasma testosterone levels were significantly decreased compared with the control group. Both ethyl acetate and xylene caused a decrease in the weight of the testes and accessory reproductive organs, as well as reducing acid phosphatase activity in the prostate and plasma testosterone levels. In contrast, toluene and methanol had no effect on organ weights, circulating testosterone levels, or on enzyme activity. Body weight was decreased by inhalation of thinner or ethyl acetate vapour. Spermatozoa levels in the epididymis were decreased by inhalation of ethyl acetate and xylene vapour. These results suggest that thinner, particularly the components ethyl acetate and xylene, interfere with the functions of the testes and accessory reproductive organ; toluene has no effect on these functions.

B. Studies reporting no developmental or reproductive toxicity

Postnatal evaluation of prenatal exposure to p-xylene in the rat.
Rosen M. B., Crofton K. M. and Chernoff N.
Toxicol Lett. 1986;34(2-3):223-9.

Pregnant Sprague-Dawley rats were exposed to either 3500 or 7000 mg/m3 p-xylene from days 7-16 of gestation. Dams were allowed to give birth, and litters were counted, weighed, and observed for external malformations on postnatal days (PD) 1 and 3. Litters were normalized to 8 pups (4 males and 4 females +/- 1) on PD4. On PD21 animals were weaned and littermates housed by sex. Body weights were recorded weekly until weaning and once every 2 weeks thereafter. Central nervous system (CNS) development was evaluated by acoustic startle response on PD13, 17, 21, and 63 as

well as figure-8 maze activity on PD22 and 65. Maternal weight gain during the treatment period was significantly less in the high-dose group. No effects were seen on litter size or weight at birth or on PD3. There were no effects of xylene exposure on growth rate. There were no treatment-related effects on acoustic startle response or figure-8 maze activity. Thus, p-xylene as administered in this study does not appear to be a selective developmental toxicant in the rat.

II. Epidemiologic Developmental and Reproductive Toxicity Studies

A. Studies reporting increased risk of adverse developmental or reproductive outcomes

i. Developmental toxicity

Laboratory work and pregnancy outcome.

Taskinen H, Kyyrönen P, Hemminki K, Hoikkala M, Lajunen K, Lindbohm ML.
J Occup Med. 1994, Mar; 36(3):311-9.

Spontaneous abortions among women working in laboratories, and congenital malformations and birth weights of the children were examined in a retrospective case-referent study. In the spontaneous abortion study there were 535 women (206 cases and 329 referents), and in the malformation study 141 women (36 cases and 105 referents). The analysis of the birth weights concerned 500 women (referents). Significant associations with spontaneous abortion were found for exposure to toluene (odds ratio [OR], 4.7, 95% confidence interval [CI], 1.4 to 15.9), xylene (OR 3.1, CI 1.3 to 7.5) and formalin (OR 3.5, CI 1.1 to 11.2) > or = 3 days a week, adjusted for the covariates. Most of the women exposed to formalin and xylene were working in pathology or histology laboratories. No association with congenital malformation was found.

ii. Female reproductive toxicity

[Effect of exposure to low concentration of benzene and its analogues on luteal function of female workers].
Chen H., Song L., Wang X. and Wang S.
Wei Sheng Yan Jiu. 2000, Nov; 29(6):351-3.

The effect of benzene and its analogues(BIA) on the luteal function of female workers was studied in a petrochemical corporation. The female workers from a chemical fiber corporation without benzene exposure were selected as controls. The levels of BIA(toluene and xylene) in the air at breathing zone were sampled and determined with

gas chromatography (GC). The menstrual function was followed up. Urine pregnanediol-3-glucuronide (PdG) and follicular stimulating hormone (FSH) were measured by enzyme immunoassay(EIA). The results showed that BIA existed in low concentration in air. The exposure could lead to a shorter length of time of luteal phase ($P < 0.05$ or $P < 0.01$) and decrease luteal progesterone level ($P < 0.05$). It was suggested that the low concentration of BIA exposure could have effect on the luteal function in exposed female workers, and urinary hormones could be used as biomarker for the influences of benzene and BIA on reproduction.

Laboratory work and pregnancy outcome.
Taskinen H, Kyyrönen P, Hemminki K, Hoikkala M, Lajunen K, Lindbohm ML.
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iii. Male reproductive toxicity

Effect of benzene, toluene, xylene on the semen quality and the function of accessory gonad of exposed workers.
Xiao G., Pan C., Cai Y., Lin H. and Fu Z.
Ind Health. 2001, Apr; 39(2):206-10.

The effects on semen and the function of accessory gonad of workers after short and long term exposure to benzene, toluene, and xylene were examined. The semen and blood of 24 married workers exposed to benzene, toluene, and xylene were collected. Routine sperm characteristic, acrosin activity, and Lactate dehydrogenase C4 (LDH-C4) relative activity were detected. The results showed that benzene, toluene, and xylene were found in the blood and semen of some ex-workers at workplaces where the air concentration of benzene, toluene, and xylene exceeded the maximum allowable concentration (MAC). No such solvents were detected in the blood and semen of workers of the control group. The sperm vitality and sperm motility decreased in the exposed workers. The mean acrosin activity, gamma-GT activity and LDH-C4 relative activity in the exposed workers were lower, and fructose concentration was higher than those in the control. There were negative correlations between sperm vitality, sperm

activity, acrosin activity, or LDH-C4 relative activity and working history. These results suggest that the mixture of these solvents could affect the sperm and the function of accessory gonad. This might be one reason of the abnormal pregnancy outcome among the wives of workers exposed to benzene, toluene, and xylene.

B. Studies reporting no increased risk of adverse developmental or reproductive outcomes

No reports were identified for this category

III. Other Relevant Information

A. Meeting Abstracts

No reports were identified for this category

C. Related articles

Association between GIS-based exposure to urban air pollution during pregnancy and birth weight in the INMA Sabadell Cohort.
Aguilera I., Guxens M., Garcia-Esteban R., Corbella T., Nieuwenhuijsen M. J., Foradada C. M. and Sunyer J. Environ Health Perspect. 2009, Aug; 117(8):1322-7.

[BTEX exposure and its health effects in pregnant women following the Hebei Spirit oil spill].
Kim B. M., Park E., LeeAn S. Y., Ha M., Kim E. J., Kwon H., Hong Y. C., Jeong W. C., Hur J., Cheong H. K., Yi J., Kim J. H., Lee B. E., Seo J. H., Chang M. H. and Ha E. H.
J Prev Med Public Health. 2009;42(2):96-103.

Toluene and P-xylene mixture exerts antagonistic effect on lipid peroxidation in vitro.
Sawicka E. and ugosz A. Int J Occup Med Environ Health. 2008;21(3):201-9.

Evidence of reproductive endocrine effects in women with occupational fuel and solvent exposures.
Reutman S. R., LeMasters G. K., Knecht E. A., Shukla R., Lockey J. E., Burroughs G. E. and Kesner J. S. Environ Health Perspect. 2002, Aug; 110(8):805-11.

Behavioral effects following subacute inhalation exposure to m-xylene or trimethylbenzene in the rat: a comparative study.
Gralewicz S. and Wiaderna D. Neurotoxicology. 2001, Feb; 22(1):79-89.

[Effects of the couple exposures to the mixed benzene on gestational processes and pregnancy outcomes].
Wang S. L., Chen Y. L., Xing H. X., Zhang J., Du B., Cao J. Z., Shi A. M., Wang D. X., Xu X. P. and Wang X. L. . Chung-Kuo Kung Kung Wei Sheng (China Public Health). 2001;17(2):126-7.

CYP 450 enzyme induction by chronic oral musk xylene in adult and developing rats.
Suter-Eichenberger R., Boelsterli U. A., Conscience-Egli M., Lichtensteiger W. and Schlumpf M. Toxicol Lett. 2000, Apr 10; 115(1):73-87.

Decreased formation of ethoxyacetic acid from ethylene glycol monoethyl ether and reduced atrophy of testes in male rats upon combined administration with toluene and xylene.
Chung W. G., Yu I. J., Park C. S., Lee K. H., Roh H. K. and Cha Y. N. Toxicol Lett. 1999, Jan 11; 104(1-2):143-50

Male reproductive effects of solvent and fuel exposure during aircraft maintenance.
Lemasters G. K., Olsen D. M., Yiin J. H., Lockey J. E., Shukla R., Selevan S. G., Schrader S. M., Toth G. P., Evenson D. P. and Huszar G. B. Reprod Toxicol. 1999 May-Jun; 13(3):155-66.

CYP 450 enzyme induction by chronic oral musk xylene in adult and developing rats.
Suter-Eichenberger R., Boelsterli U. A., Conscience-Egli M., Lichtensteiger W. and Schlumpf M.. Toxicol Lett. 1999, Dec 20; 111(1-2):117-32.

Bioaccumulation of musk xylene (MX) in developing and adult rats of both sexes.
Suter-Eichenbeger R., Altorfer H., Lichtensteiger W. and Schlumpf M. Chemosphere. 1998, Jun; 36(13):2747-62.

The effect of ageing and in vitro exposure to xylene and KCl on [Ca2+]i in synaptosomes from rats exposed prenatally to xylene.
Edelfors S., Hass U., Ravn-Jonsen A. and Lund S. P. Pharmacol Toxicol. 1996, Jun; 78(6):409-12

Induction of birth defects by exposure to solvents: an in vitro study.
Brown-Woodman P. D., Webster W. S., Huq F., Herlihy C., Hayes L. C. and Picker K. Teratology. 1995;51(4):288.

In vitro assessment of individual and interactive effects of aromatic hydrocarbons on embryonic development of the rat.
Brown-Woodman P. D., Webster W. S., Picker K. and Huq F. Reprod Toxicol. 1994 Mar-Apr; 8(2):121-35.

Assessment of interactive effects of the aromatic hydrocarbons toluene, xylene and benzene on rat embryonic development in vitro.
Brown-Woodman P. D., Webster W. S., Huq F. and Picker K. Teratology. 1992;45(3):326.

Embryotoxicity of xylene and toluene: an in vitro study.
Brown-Woodman P. D., Webster W. S., Picker K. and Ritchie H. E. Ind Health. 1991;29(4):139-52.

Effect of the aromatic hydrocarbons toluene, xylene and benzene on rat embryonic development in vitro.
Brown-Woodman P. D., Webster W. S., Ritchie H. and Picker K. Teratology. 1991;44(4):479.

An in vitro study for the teratogenic potential of xylene and toluene.
Brown-Woodman P. D., Webster W. S., Picker K. and Ritchie H. E. Teratology. 1990;42(3):328.

Effects on reproduction of styrene, toluene and xylene
Freij L. NTIS Technical Report (NTIS/PB95-211264) (KEMI-2-90) 1990;:73 pp.

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