REVIEW OF REPRODUCTIVE AND DEVELOPMENTAL TOXICITY INDUCED BY ORGANOTINS IN AQUATIC ORGANISMS AND EXPERIMENTAL ANIMALS

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Introduction

Organotins are chemicals widely used in agriculture and industry. Tetrasubstituted organotins are mainly used as intermediates in the preparation of other organotin compounds. Trisubstituted organotins have biocidal properties and are used in agriculture as fungicides and acaricides, and as rodent repellents and mulluscicides, and they are widely used as antifoulants in ship paints and underwater coatings, especially, triphenyltins (TPTs) and tributyltins (TBTs) have been used extensively in antifouling products as algaecides and mulluscicides. Disubstituted organotins are commercially the most important derivatives, and are mainly used in the plastics industry, particularly as heat and light stabilizers for poly(vinyl chloride) (PVC) plastics to prevent degradation of the polymer during melting and forming of the resin into its final products, as catalysts in the production of polyurethane foams, and as vulcanizing agents for silicone rubbers. Monosubstituted organotins are used as stabilizers in PVC films.

Widespread use of organotins has caused increasing amounts to be released into the environment. The most important non-pesticidal route of entry of organotins into the environment is through leaching of organotin-stabilized PVC in water, and the use in antifouling agents, resulting in the introduction of organotin into the aquatic environment. Data are available regarding the detection of butyltins and phenyltins in aquatic marine organisms[1] and marine products[2,3]. Food chain bioamplification of butyltin in oysters[4], mud crabs[5], marine mussels[6], chinook salmons[7], dolphins, tunas, and sharks[8] and of phenyltin in carps[9] and horseshoe crabs[10] has been reported. These findings indicate that organotins accumulate in the food chain and are bioconcentrated, and that humans can be exposed to organotins via seafood. Recently, the daily intakes in Shiga prefecture in Japan were reported to be 0.7-5.4 μg in 1991 and 0.7-1.3 μg in 1992 for TPT and 4.7-6.9 μg in 1991 and 2.2-6.7 μg in 1992 for TBT[2]. It is also reported that the daily intakes in Japanese consumers, based on analysis with the 1998 total diet samples, were 0.09 μg for TPT, 0 μg for diphenyltin (DPT), 1.7 μg for TBT, and 0.45 μg for dibutyltin (DBT)[3]. These values are lower than the acceptable daily intake for TPT of the JMPR, 25 μg[11], and the guidance value for oral exposure to tributyltin oxide (TBTO), 18 μg[12] (IPCS 1999). Thus, the levels of organotin compounds in seafood are not considered to be sufficiently high to affect human health. However, Belfroid et al. (2000)[13] noted that more research on residual TBT levels in seafood was needed before a definitive conclusion on possible health risks could be drawn.

Although the toxicity of organotins has been extensively reviewed, the reproductive and developmental toxicity of organotins is not well understood. We summarized the data of the studies

on reproductive and developmental toxicity of organotins in aquatic organisms and experimental animals.

Effects on aquatic organisms

TBT or TPT causes the imposition of male sex organs termed "imposex" on female mud snails above the concentration of about 1 ng/L (Sn) in seawater, but DBT or monobutyltin (MBT) does not induce imposex. The intensity is characterized by a classification system based on the VAS Deferens Sequence Index (VDSI), and advanced phase of imposex and sterilization with gross morphological changes would be irreversible. The biochemical mechanism studies suggested that the induced either neurotropic hormone or androgen titer would lead to imposex induction at extremely low dose of TBT.

Also TBT and TPT exposure in early life stages of fishes caused changes in embryonic development, impairment of morphological development, delay or inhibition of hatching, and reduction in fecundity and sperm counts as reproductive effects. Such reproductive and developmental defects were also found in other species. The impaired reproduction and subsequent population decline in a variety of aquatic organism by organotins are of important issue on aquatic ecosystem.

Effects on experimental animals

Reproductive effects of phenyltins: TPTs caused decrease in male fertility of rats due to degenerative changes in testicular tissue which were associated with marked decrease in food consumption. Complete recovery of fertility and impairment of the spermatogenesis were noted following withdrawal of treatment. Female reproductive failure induced by TPTs is more prominent. The harmful effects of TPTs on the ovaries such as decreased number of the mature follicles and corpora lutea were presented after 5days treatment before any significant effects on body weight gain in rats.

Triphenyltin chloride (TPTCl) during early pregnancy caused implantation failure in rats and TPTCl had greater antiimplantation effects when administered during the preimplantation period. The implantation failure due to TPTCl is suggested to be mediated via the suppression of uterine decidualization and correlated with the reduction in serum progesterone levels. Implantation failure and suppression of uterine decidualization accompanied with decreased levels of serum progesterone were also observed in rats given DPT, major metabolite of TPT.

Developmental effects of phenyltins: Maternal exposure to TPTs caused embryonic/fetal death and suppression of fetal growth at maternal toxic doses in rats. TPTs may cause reduction of fetal ossification at non-maternal toxic dose. TPTs did not induce an increased number of fetal malformations even at doses produced overt maternal toxicity. Behavioral changes were reported in postnatal offspring of maternal rats received TPTs during pregnancy at doses which did not cause overt maternal toxicity.

Reproductive effects of buthyltins: In a rat two-generation reproductive toxicity study, tributyltin chloride (TBTCl) affected the male and female reproductive system. TBTCl caused decreases in weights of the testis, epididymis and ventral prostate, and spermatid and sperm counts in male offspring. The serum estradiol levels were decreased in male offspring, but serum levels of

luteinizing hormone and testosterone were not decreased. Total number and average body weight of pups, and live birth index were decreased. Delayed vaginal opening and impaired estrous cyclicity were found in female offspring. The anogenital distance (AGD) was increased at 2 mg/kg in female offspring. These results suggest TBTCl may be a weak aromatase inhibitor in males and may exert a musculinizing effect on females.

TBTCl during early pregnancy caused implantation failure in rats. Implantation failure due to TBTCl may be mediated via the suppression of uterine decidualization and correlated with the reduction in serum progesterone levels.

As for DBT, a major metabolite of TBT, implantation failure was also observed following administration of dibutyltin dichloride (DBTCl), at lower doses than TBTCl, during early pregnancy. Suppression of uterine decidualization accompanied with reduced levels of serum progesterone was also observed in pseudopregnant rats given DBTCl at doses induced implantation failure. Administration of progesterone protected, at least in part, against the DBTCl-induced implantation failure. Monobutyltin trichloride (MBTCl) during early pregnancy did not cause pre- or postimplantation embryonic loss even at 903 mg/kg. These results suggest that DBT may be responsible for the TBT-induced implantation failure and decrease in serum progesterone levels may be a primary factor for implantation failure due to butyltins.

Developmental effects of buthyltins: Maternal exposure during pregnancy to TBTs, such as TBTO, tributyltin acetate (TBTA), and TBTCl, caused embryonic/fetal deaths and suppression of fetal growth at maternal toxic doses in mice and rats. At severely maternal toxic doses of TBTs, cleft palate was produced in mouse and rat fetuses. Behavioral changes were also reported in postnatal offspring of rats received TBTs during pregnancy at doses which did not cause overt maternal toxicity.

Pregnant rats were gavaged with TBTCl at 0.025-2.5 mg/kg from day 8 of pregnancy until weaning and offspring were gavaged with the same dose of TBTCl given to their mothers until adulthood. No effects of TBTCl on maternal body weight or food consumption, litter size, sex ratio or postnatal survival rate were found. Reduced serum thyroxine levels in male offspring at 2.5 mg/kg and decreased weight of the spleen and thymus at 0.25 mg/kg were observed. Significant effects on growth profiles in male and female offspring, and decreased liver weights and elevated serum GGT levels in female offspring were noted even at 0.025 mg/kg.

The teratogenicity of DBTs has been reported in a single species. DBT derivatives with different anions, such as dichloride, diacetate, maleate, dilaurate, oxide and 3-hydroxy-DBT-dilairate, produced fetal malformations when administered during organogenesis in rats. DBT may increase the incidence of fetal malformations, such as defect of the mandible, cleft lower lip, ankyloglossia, deformity of the vertebral column and ribs and anomaly of tail, at marginal doses induced maternal toxicity. Developing rat embryos were not susceptible to teratogenicity of DBTCl on day 6, and that day 7 was the earliest susceptible period, day 8 was the most susceptible period and day 9 was no longer a susceptible period to the teratogenicity of DBTCl.

Administration of tetrabutyltin (TeBT) on days 13-15 of pregnancy caused an increased incidence of cleft palate at extremely high dose in rats. There were differences in the manifestation and degree of developmental toxicity among TeBT, TBT, DBT, and MBT. The developmental toxicity studies on butyltins suggest that the teratogenicity of DBT is different from those of TeBT, TBT, and MBT in its mode of action, because the susceptible period for teratogenicity and types of malformations induced by DBT are different from those induced by tetra-, tri, and monosubstituted organotins.

DBTCl exerts dysmorphogenic effects on postimplantation embryos in cultured rat embryos. The dysmorphogenic concentrations of DBTCl in rat embryos cultured were well within the range of levels detected in maternal blood after the administration of a teratogenic dose of DBT. In vitro exposure to DBTCl interfered with normal development of embryos during three different stages of organogenesis and that the susceptibility to the embryotoxicity including dysmorphogenic potential of DBTCl varies with developmental stage. The phase specificity for the in vivo teratogenesis of DBTCl may be attributable to a decline in the susceptibility of embryos to the dysmorphogenesis of DBTCl with advancing development. The findings of in vivo and in vitro studies suggest that DBT itself is a causative agent in DBT teratogenesis.

Developmental effects of miscellaneous organotins: Prenatal and/or postnatal exposure to trimethytin chloride (TMTCl) or monomethyltin trichloride (MMTCl) caused learning deficiency in postnatal rat offspring, but no difference between the weights of control and experimental animals in suckling pups or their dams was found. The learning deficiency induced by prenatal TMTCl may be due to hippocampus lesions. Maternal ip injection of TMTCl adversely affected survival and growth of offspring. Prenatal treatment of trihexyltin chloride (THTCl) is also reported to induce behavioral changes in postnatal offspring. Increased number of cleft palate was observed in fetuses of rats given dimethyltin chloride (DMTCl) during organogenesis at severely maternal toxic dose. A mixture of dioctyltin diisooctylthioglycolate (DOTTG) and monooctyltin triisooctylthioglycolate (MOTTG) caused increases in the incidence of fetal malformations at maternal toxic doses and of skeletal variation at non-maternal toxic doses in mice.

Conclusions

TBT or TPT causes the imposition of male sex organs termed "imposex" on female mud snails above the concentration of about 1 ng/L (Sn) in seawater, but DBT or MPT does not induce imposex. The intensity is characterized by a classification system based on the VDSI, and advanced phase of imposex and sterilization with gross morphological changes would be irreversible. The biochemical mechanism studies suggested that the induced either neurotropic hormone or androgen titer would lead to imposex induction at extremely low dose of TBT. Also TBT and TPT exposure in early life stages of fishes caused changes in embryonic development, impairment of morphological development, delay or inhibition of hatching, and reduction in fecundity and sperm counts as reproductive effects. Such reproductive and developmental defects were also found in other species. The impaired reproduction and subsequent population decline in a variety of aquatic organism by organotins are of important issue on aquatic ecosystem.

TPTs caused decrease in fertility due to degenerative changes in testicular tissue and ovarian impairment. TPTCl and DPTCl during early pregnancy caused implantation failure which was suggested to be mediated via the suppression of uterine decidualization and correlated with the reduction in serum progesterone levels. TPTs during organogenesis caused embryonic/fetal death and suppression of fetal growth at maternal toxic doses. TPTs did not increase in the incidence of fetal malformations even at doses produced overt maternal toxicity. Behavioral changes were observed in postnatal offspring of rats received TPTs during pregnancy at doses which did not cause overt maternal toxicity. TBTCl caused decreased weights of the male reproductive organs, decreased counts of spermatids and sperms, and decrease in serum estradiol levels, delayed vaginal opening, impaired estrous cyclicity, and increased female AGD in a rat two-generation reproductive toxicity study. TBTCl or DBTCl produced implantation failure when administered

during early pregnancy. Implantation failure may be mediated via the suppression of uterine decidualization and correlated with the reduction in serum progesterone levels. MBTCl during early pregnancy did not cause pre- or postimplantation loss. Maternal exposure to TBTs produced embryonic/fetal deaths, suppression of fetal growth, and cleft palate at maternal toxic doses. Behavioral changes were also reported in postnatal offspring of rats received TBTs during pregnancy at doses which did not cause overt maternal toxicity. Significant effects on growth profiles, and decreased liver weights and elevated serum GGT levels were noted in offspring of rats given TBTCl pre- and postnatally even at 0.025 mg/kg. DBTs produced fetal malformations when administered during organogenesis in rats. Rat embryos are the most susceptible to teratogenic effects of DBT on day 8 of pregnancy after maternal exposure. The teratogenic effects of DBT are different from those of TeBT, TBT, and MBT in its mode of action. DBTCl exerts dysmorphogenic effects on postimplantation embryos in vitro. The phase specificity for the in vivo teratogenic effects of DBTCl may be attributable to a decline in the susceptibility of embryos to the dysmorphogenesis of DBTCl with advancing development. The findings of in vivo and in vitro studies in rats suggest that DBT itself is a causative agent in of DBT teratogenesis. Studies in additional species would be of great value in evaluating developmental toxicity of DBTs. Prenatal and/or postnatal exposure to TMTCl or THTCl caused behavioral changes in postnatal rat offspring. A mixture of DOTTG and MOTTG is developmentally toxic in mice. Increased number of cleft palate was reported in fetuses of rats given DMTCl during organogenesis at severely maternal toxic dose. Behavioral changes in postnatal pups of rats given organotins prenatally and/or postnatally may be susceptible parameters for developmental toxicity of organotins.

To better understand the reproductive and developmental toxicity of organotins, further studies are needed to clarify the biochemical mechanisms of imposex, the teratogenicity of DBTs and reproductive and developmental toxicity induced by low dose of TBT.

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