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Toxicology of Octabromobiphenyl and Decabromodiphenyl Oxide

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Decabromodiphenyl oxide (DBDPO) and octabromobiphenyl (OBBP) perform well as fire-retardant additives for thermoplastics. Both compounds have low acute oral toxicity and low skin absorption toxicity. They are neither primary skin irritants or skin sensitizers and are only mildly irritating to the eyes. A 30-day dietary feeding study in rats established 8 mg DBDPO/kg-day as an unequivocal no-effect level and 80 mg/kg-day as a marginal effect level. A no-effect level was not established for OBBP in a comparative study. A 2-yr rat study providing 0.1 mg DBDPO/kg-day in the diet revealed the bromine concentration reached a plateau in the liver within 30 days, while the concentration in adipose tissue slowly increased. A comparable OBBP study revealed bromine concentration in the liver and adipose tissue increased steadily and rapidly with no attainment of a plateau during 180 days of the study. Neither compopnd produced an accumulation of bromine in other tissues. After administration of ^{14}C DBDPO, all ^{14}C activity was eliminated via the feces within 2 days. After administration of ^{14}C OBBP, 62% was eliminated with a half-life of less than 24 hr; the half-life for the remainder was greater than 16 days. In a teratology study, 10, 100, or 1000 mg DBDPO/kg-day had no effect in rats. Reproductive capacity of rats was not effected at 3, 30, or 100 mg DBDPO/kg-day. No effects were observed on cytogenetic examination of bone marrow cells of parents and weanlings from the reproduction study.

Introduction

Flame retardancy is required for high performance thermoplastic resins because of their use in electrical and high temperature applications. Two compounds which meet stringent thermal stability requirements for these ap-applications are decabromodiphenyl oxide (DBDPO) and octabromobiphenyl (OBBP). DBDPO has also found acceptance as a flame-retardant (FR) agent for high-impact polystyrene, ABS, polyethylene, adhesives, thermoset polymer applications of epoxy resins, and unsaturated polyesters and in textile coating formulations. Since the toxicological properties of fire-retardant chemicals are a major factor in determining suitability for large scale use, the studies summarized in this paper were undertaken. The studies were intended to evaluate the toxicity of the materials and assess the potential hazards associated with their manufacture and use and to determine if these materials, like the structurally similar polychlorinated biphenyls, are absorbed and retained by the body.

Materials

The structure and properties of commercially produced decabromodiphenyl oxide (DBDPO) and octabromobiphenyl (OBBP) are summarized in Table 1.

The composition of the OBBP and DBDPO

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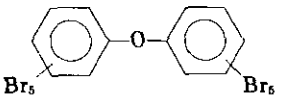
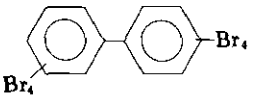
Table 1. Properties of commercial decabromodiphenyl oxide (DBDPO) and octabromobiphenyl (OBBP).

	DBDPO	OBBP
Structure		
Empirical formula	$C_{12}Br_{10}O$	$C_{12}Br_8H_2$
Bromine, %	83	82
Molecular weight	960	786
Melting range, °C	290–306	200–250
Decomposition point (DTA), °C	425	435
Volatility, TGA (10°C/min) °C		
< 1% wt. loss	300	250
<10% wt. loss	330	310
<50% wt. loss	370	350
Vapor pressure, mm Hg		
At 250°C	<1	
At 278°C	2	
At 306°C	5	
Solubility at 25°C		
Water, ppb	20–30	20–30
Cottonseed oil, ppm	600	1700
Solubility in organic solvents, g/100 g solvent		
Acetone	0.05	1.80
Benzene	0.48	8.10
Chlorobenzene	0.60	18.70
Methylene bromide	0.42	7.40
Methylene chloride	0.49	3.90
o-Xylene	0.87	10.00
Octanol: water partition coefficient	172,000	340,000

samples used in the toxicological studies was determined by vapor phase chromatography and mass spectrophotometry. The OBBP sample contained 45.2% OBBP, 47.4% nonabromobiphenyl, 5.7% decabromobiphenyl, and 1.8% heptabromobiphenyl. The composition of the sample of DBDPO (Dow FR–300–BA, Specification Number D37968) was 77.4% DBDPO, 21.8% nonabromodiphenyl oxide, and 0.8% octabromodiphenyl oxide.

Experimental

Range-finding acute oral studies on OBBP and DBDPO were conducted on female Sprague-Dawley rats (Spartan strain); New Zealand albino rabbits were used in routine eye and skin irritation studies. A repeated insult patch test was conducted on 50 human subjects to assess the skin sensitization potential of DBDPO. The rabbit ear bioassay test for bromacnegenic activity was conducted on both materials according to published procedures (*1,2*). Thirty-day feeding studies utilized male Sprague-Dawley rats which were maintained on diets providing 800, 80, 8, or 0 mg of OBBP or DBDPO/kg-day. A 2-yr dietary feeding study in male and female rats providing dose levels of 1.0, 0.1, 0.01, or 0 mg of DBDPO/kg-day is on-going. A comparable study with OBBP was terminated after 8 months because of the likelihood that this material would bioaccumulate in the environment. Parameters monitored in the dietary feeding studies included the following: body weights, food consumption, appearance and demeanor, routine hematologic determinations, urinalysis, serum enzyme activity, organ weights, and gross and histopathological examination of tissues. In addition, at various times during a 2-yr period, tissues of rats receiving the aforementioned dietary levels of OBBP or DBDPO were analyzed for bromine by neutron activation analysis. Studies on the elimination of bromine from tissues were conducted on rats maintained for 90 days on diets containing 1.0 mg of OBBP or DBDPO/kg-day and then placed on a diet of untreated feed for designated periods up to 90 days for recovery.

^{14}C-labeled OBBP or DBDPO, suspended in corn oil, was administered to male and female Sprague-Dawley rats at a dose of 1 mg/kg, and excretion of the radioactivity was measured at 24-hr intervals over a 16-day period. Radioactivity in various tissues of the ^{14}C-OBBP- or ^{14}C-DBDPO-treated rats was determined on days 1, 3, and 16. Pregnant female Sprague-Dawley rats on a teratology study were administered 1000, 100, 10, or 0 mg of DBDPO/kg on days 6–15 of gestation followed by cesarean section on day 21 of gestation. The maternal animals were evaluated for appearance and demeanor, food consumption, body and liver weights, and bromine concentration in liver tissue. Teratological examinations for effects on fetal body measurements, incidence of fetal resorptions and anomalies were conducted. Bromine concentration in fetal liver tissue was determined. Male and female rats on a reproduction study were provided diets containing 100, 30, 3, or 0 mg DBDPO/kg-day for 60 days before being mated. Parameters monitored included the following: body weights, food consumption, length of time between the first day of cohabitation and parturition, number of live and dead newborn, number of live pups at days 1, 7, 14, and 21, litter weights at days 1, 7, and 14, individual weanling weights at day 21, sex of each weanling at days 1 and 21, abnormalities noted on day 21, organ weights, and gross and pathological examination of tissues from parental weanling animals and cytogenetic examination of bone marrow cells from parental and weanling animals.

Results

Acute Oral Toxicity of OBBP and DBDPO

Intragastric intubation of a single dose of a 10% corn oil suspension of OBBP or DBDPO to female rats that had been deprived of food for approximately 15 hr resulted in the survival of all rats at dose levels of 126, 252, 500, 1000, or 2000 mg/kg. There were no indications of toxicity among the OBBP or DBDPO treated rats directly after intubation or during the 14-day post-treatment observation period. All animals displayed body weight gains over the 14-day observation period. Gross pathological examination of one rat/dose level of OBBP or DBDPO, 24 hr after treatment, revealed no detectable pathological changes.

Skin Irritation of OBBP and DBDPO

Skin irritation studies conducted on shaved skin of rabbits showed that OBBP and DBDPO, as dry solids, caused essentially no response on intact skin and a slight erythematous and edematous response on abraded skin after a single confined exposure of 24 hr. Repeating the exposures to intact skin for 5 days/week for 2 weeks and to abraded skin for 3 days did not alter the responses. OBBP moistened with water caused no response on intact skin and a moderate erythematous and slight edematous response on abraded skin after 24 hr of confined contact. Repeating the exposures caused a slight erythematous response on the intact skin and no alteration in the response of abraded skin. After cessation of treatment, the erythematous and edematous responses subsided and at the termination of the study all skin sites were normal in appearance. No changes in appearance or demeanor, or effects on body weights were observed.

Eye Irritation of OBBP and DBDPO

Eye irritation studies conducted on rabbits showed that OBBP or DBDPO, as dry solids, caused transient irritation of the conjunctival membranes of washed and unwashed eyes. The cornea, iris, and lens were unaffected. The eyes of the rabbits showed no conjunctival membrane irritation 24 hr after instillation of either experimental material.

Human Skin Sensitization Study on DBDPO

Repeated application of a homogenous 5% suspenion of DBDPO in petrolatum, three times per week for three weeks, to the skin of 50 human subjects resulted (*3*) in no skin sensitization response during the "sensitizing" period or on challenge 2 weeks subsequent to the last application.

Bromacnegenic Activity of OBBP and DBDPO

Bioassay tests for possible bromacnegenic activity conducted on the ear of rabbits showed that OBBP or DBDPO, as 10% chloroform solutions, caused a slight erythematous response and slight exfoliation during the month-long

study. There was no indication of the bromacne response on the ears treated with either experimental material at any time during or at the termination of the study.

30-Day Rat Dietary Feeding Studies on OBBP and DBDPO

Male rats maintained on diets containing 1.0, 0.1, 0.01, or 0% OBBP or DBDPO providing approximate dose levels of 800, 80, 8, or 0 mg/kg-day showed no changes in appearance or demeanor during the 30-day study. Inclusion of OBBP or DBDPO at any level in the diets did not influence the food consumption or body weight gains of the respective experimental animals. Hematology studies conducted during the terminal week of the study showed statistically significant decreased packed cell volume and total red blood cell count of rats on the 1% dietary level of OBBP. The hematological determinations on the rats on the 0.1 and 0.01% dietary levels and on the rats receiving diets containing 1.0% DBDPO were not statistically different than the rats on the control diet.

Urinalyses made during the terminal week of the study showed no difference in total solids, pH, sugar, albumin, occult blood, and ketones of rats on diets containing OBBP or DBDPO when compared with rats on the control diet.

A comparison of organ weights showed no dose-related statistical difference in heart, testes, or brain from rats on diets containing OBBP or DBDPO or in the weight of kidneys from rats on diets containing DBDPO. Enlarged livers were found in the rats on all dietary levels of OBBP and those rats on the 1.0 and 0.1% levels of DBDPO. Increased kidney weights were found in rats on diets containing 1.0 and 0.1% OBBP.

Gross pathological changes that were observed at necropsy were limited to dose-related liver enlargement in rats at all dose levels of OBBP and those on the 1.0% dietary level of DBDPO. Kidney changes, consisting of petichial hemorrhage, enlargement, and mottling, were noted only in some of the rats on diets containing OBBP.

The histopathological examination of organs and tissues of the rats on the experimental diets revealed liver and kidney lesions at all levels of OBBP and at the 1.0% dietary level of DBDPO. The liver lesions consisted of centrilobular cytoplasmic enlargement and vacuolation; the kidney lesions consisted of hyaline degenerative cytoplasmic changes. The other dose related pathological finding was thyroid hyperplasia which was observed in rats on all levels of OBBP and those rats on the 1.0 and 0.1% dietary levels of DBDPO.

^{14}C Metabolism Studies on OBBP and DBDPO

^{14}C-labeled OBBP and DBDPO used in these studies had specific activities of 1.1 μCi/mg. The level of radioactivity found in the urine and expired air of three male and three female rats dosed with 1.0 mg of OBBP or DBDPO/kg suspended in corn oil and measured at 24-hr intervals over a 16-day period was less than 1%. The principal route of excretion for these materials was via the feces. The respective rates of excretion of OBBP or DBDPO were the same for both sexes. The mean values of ^{14}C activity found in the feces of the group of three male rats/experimental material are graphed in Figure 1. Within the first 24 hr, 90.6% $\pm$ 1.21 (mean and standard error) of the ^{14}C activity of the dose administered to the DBDPO-treated rats was found in the feces, and 99+% of the ^{14}C activity was accounted for by day 2 of the study.

In contrast, 61.9% $\pm$ 2.39 of the ^{14}C activity administered to the OBBP-treated rats was found in the feces after the first 24 hr. From day 2 through day 16, there was a gradual elimination of approximately 11% in addition, 7% of which was accounted for during the second 24-hr period after treatment. At the termination of the study, on day 16, 26.42% $\pm$ 1.43 of the ^{14}C activity in the administered dose had not been recovered in the excreta.

Examination for radioactivity of various tissues taken from three male rats per time period following administration of the experimental materials, revealed ^{14}C activity in all tissues taken from the OBBP-treated rats on day 1 and at lower levels in tissues taken from the DBDPO-treated rats.

On day 16, ^{14}C activity was found in the adrenals, adipose tissue, heart, and skin at levels ranging from 0.14 to 0.25% of the administered dose per gram of tissue from the OBBP-treated rats. Lesser amounts were found in liver, pancreas, and spleen (0.01% $\pm$ 0.00, 0.06% $\pm$ 0.07, and 0.03 $\pm$ 0.04, respectively).

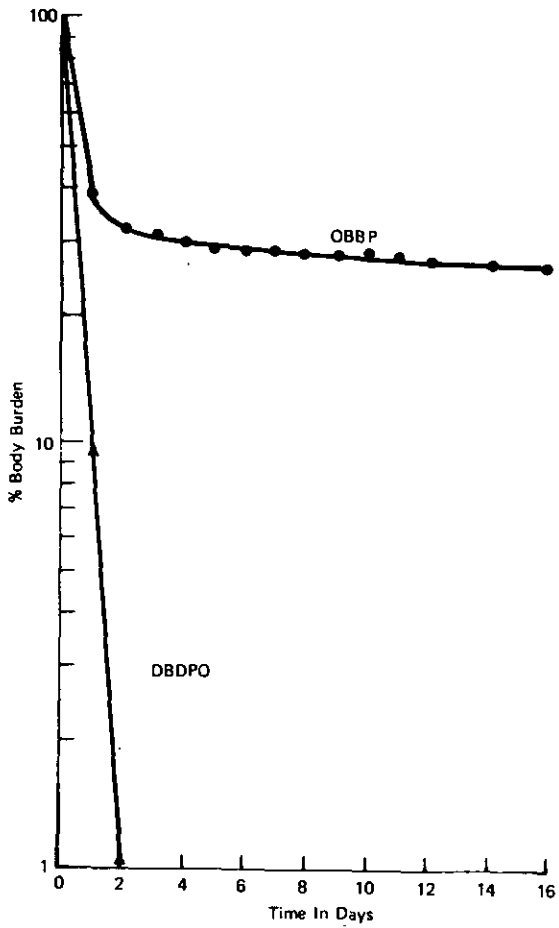


FIGURE 1. ^{14}C Activity remaining in the body as a function of time following the administration of 1.0 mg of labeled octabromobiphenyl or decabromobiphenyl oxide/kg of three male rats.

In contrast, the tissues taken from DBDPO-treated rats on day 16 showed no ^{14}C activity with the exception of the adrenal (0.01% ± 0.06 of the dose administered/gram of tissue) and splenic tissue (0.06% ± 0.07 of dose administered/gram of tissue). The ^{14}C activity in these tissues was at the limit of detection.

Two-Year Dietary Feeding Studies on OBBP and DBDPO

Eighteen months into the 2-yr study on DBDPO, the rats have shown no overt indications of adverse effects due to treatment. There have been no dose-related deaths; the body weights and food consumption of the rats on the experimental diets are not different than the control rats. Hematological determinations and urinalyses on five rats/sex/dose level at 1 yr were unremarkable.

Rats maintained for 8 months on the OBBP diets likewise showed no overt indications of adverse effects due to treatment. There were no dose-related deaths; the body weights and food consumption of the rats on the experimental diets were not different than the controls. Organ weight measurements taken at necropsy showed increased absolute and relative liver weights at the highest dose level. The findings of the other parameters were not different than the controls.

Tissue Accumulation Studies on Rats Maintained on Diets Containing OBBP or DBDPO

These studies designed to run concomitantly with the 2-yr dietary feeding studies are ongoing. Male and female rats maintained on diets providing 1.0, 0.1, 0.01, and 0 mg of OBBP and DBDPO/kg-day during the first 180 days of the study have shown that the bromine concentration in kidney, skeletal muscle, serum, and testes of the treated rats was not different from that of controls. Subsequent analyses of these tissues were, therefore, not conducted. The mean bromine content of liver and adipose tissue of rats on receiving 0.1 mg/kg-day of OBBP or DBDPO for 180 days is presented in Figures 2 and 3,

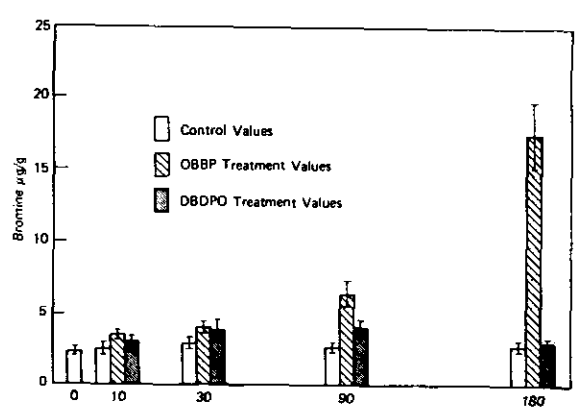


FIGURE 2. Bromine content of liver tissue from rats maintained on diets providing a dose of 0.1 mg/kg-day of octabromobiphenyl or decabromodiphenyl oxide.

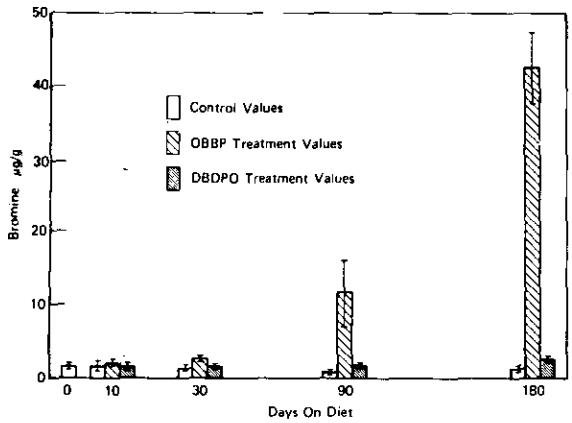


FIGURE 3. Bromine content of adipose tissue from rats maintained on diets providing a dose of 0.1 mg/kg-day of octabromobiphenyl or decabromodiphenyl oxide.

respectively. On the basis of regression analysis there was obviously an increase in the bromine concentration in these tissues of the OBBP-treated rats. Statistical analysis by use of the Student's t test showed that the bromine concentration in the adipose and liver tissue of the OBBP-treated rats was significantly increased at the $p<0.01$ level on day 180 when compared with the controls. The bromine content of the liver of DBDPO-treated rats was not significantly different from the control, whereas the bromine content of the adipose tissue from these rats was statistically increased at the $p<0.05$ level when the data were analyzed for difference in slope by using a log linear relationship. However, analyses made after 12 months on the DBDPO diets showed the bromine concentration in the adipose tissue as well as in the liver was not increased when compared with the controls.

Studies on the Elimination of Bromine from Tissues of Rats Maintained on Diets Containing OBBP or DBDPO

Male rats maintained for 90 days on diets providing a dose of 1.0 mg of OBBP or DBDPO/kg-day and then placed on control diets of untreated feed were sacrificed on the last day on the experimental diets, recovery day 0, and on recovery days 10, 30, 60, and 90. Kidney, serum, adipose tissue, and liver tissue were analyzed for bromine by neutron activation analysis. On recovery day 0, there was no

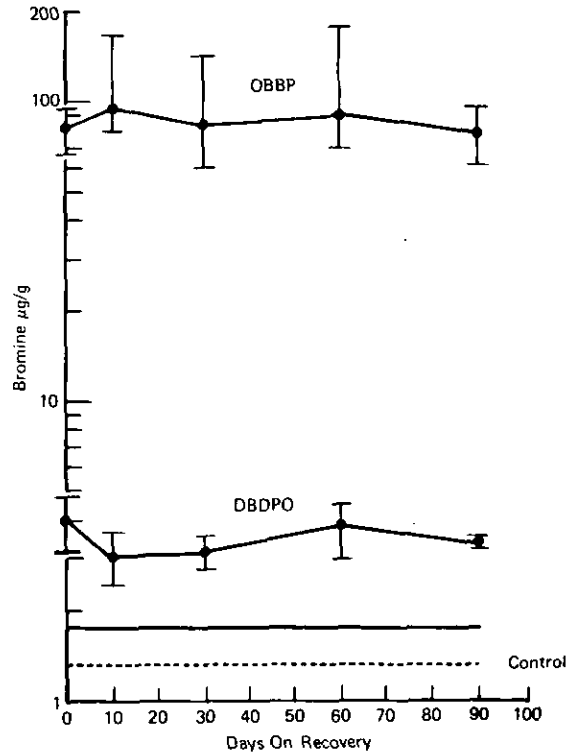


FIGURE 4. Bromine content of adipose tissue from rats on recovery following 90 days on diets providing 1.0 mg/kg-day of octabromobiphenyl or decabromodiphenyl oxide.

difference in bromine content in kidney or serum of rats on the OBBP or DBDPO diets when compared with the respective tissues of control rats. The bromine content in adipose and liver tissue on the various recovery days is given in Figures 4 and 5. Higher levels of bromine were found in these tissues of the OBBP-treated rats than in the respective tissues of DBDPO-treated rats. The respective bromine concentrations in the adipose tissue of the OBBP- and DBDPO-treated rats remained unchanged during the recovery period. There was partial elimination of bromine from the livers of the OBBP-treated rats during the first 30 days on recovery, whereas after 10 days on recovery the bromine concentration in the liver of the DBDPO rats did not differ from that of control liver tissue.

Teratology Study on DBDPO

Daily intubation, by intragastric gavage, of pregnant females on gestation days 6–15, with

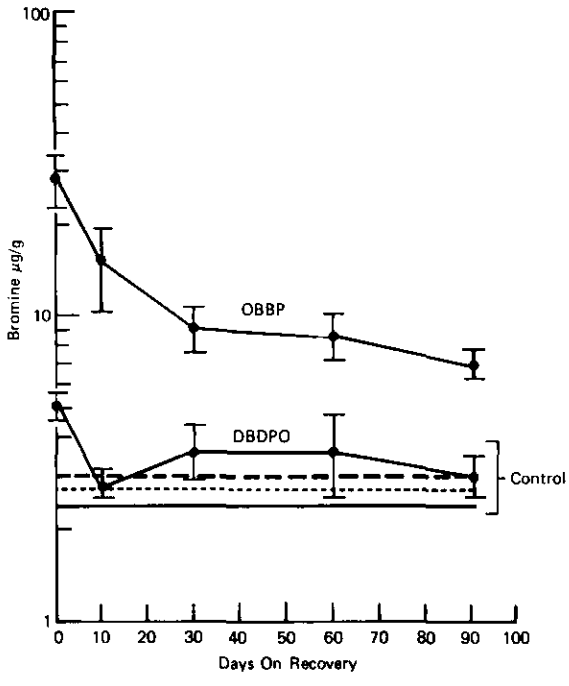


FIGURE 5. Bromine content of liver tissue from rats on recovery following 90 days on diets providing 1.0 mg/kg-day of octabromobiphenyl or decabromodiphenyl oxide.

1000, 100, 10, or 0 mg of DBDPO/kg, suspended in corn oil, caused no teratogenic response at any dose level. There were no indications of toxicity among the rats during gestation. The maternal body weights and food consumption of the DBDPO treated rats did not differ from control rats.

The terminal liver weight of the DBDPO-treated rats, obtained at the time of cesarean section, were not different from those of the controls. Similarly, no differences were seen between the treated and control rats with respect to the position and number of fetuses *in utero;* the number of corpora lutea; individual pup weight, crown rump ratio and male/female sex ratio. Significant incidences in resorptions occurred at the low dose levels but not at the high dose level.

No gross external abnormalities were seen in the fetuses from dams treated at any dose level of DBDPO. Soft tissue (*4*) and skeletal examinations (*5*) revealed an increased number of litters with subcutaneous edema and delayed ossification of normally developed bones of the skull of the fetuses of dams at the 1000 mg/kg level of DBDPO but not at the 100 mg/kg level.

Analysis of the maternal and fetal livers for bromine revealed statistically significant increased concentration in the livers of the maternal anmials receiving 1000 mg/kg-day of DBDPO. The concentrations in maternal livers at the two lower dose levels were not different from those of the controls. Likewise, there was no difference in the bromine concentration in the livers of the fetuses from dams receiving any dose level of DBDPO when compared with the controls.

Reproduction Study on DBDPO

The reproductive capacity of rats was not affected by diets providing 100, 30, or 3 mg/kg-day of DBDPO given for 90 days prior to mating as well as during mating, gestation and lactation. The per cent and number of pregnancies, pup survival indices, neonatal body weights, male/female ratio on day 21, and the length of time between the first day of cohabitation and delivery were not affected by the inclusion of DBDPO in the diets. Furthermore, examination of the neonates at weaning revealed no treatment-related effects. Cytogenetic examination of bone marrow cells taken at necropsy from the femur of the treated parental animals as well as from the neonates at weaning showed no increase in cytogenetic aberrations when compared with controls.

Summary and Discussion of the Toxicological Investigations

Octabromobiphenyl and decabromodiphenyl oxide may be considered to present a low degree of hazard from acute exposure. Both experimental materials are low in acute oral toxicity. They are neither eye nor skin irritants nor skin sensitizers (*3,6*). OBBP and DBDPO are not absorbed through the skin (*6*) in acutely toxic amounts, and they do not possess bromacnegenic activity.

Dietary feeding studies conducted over a wide range of dose levels for 30 days to elucidate the potential hazard that might be incurred through long-term repeated exposure, resulted in an unequivocal "no-effect" level of 0.01%

in the diet (approximately 8 mg/kg-day) for DBDPO, with a marginal effect level of 0.1% (approximately 80 mg/kg-day). In contrast, a no-effect level was not established for OBBP in a 30-day period at these high dose levels. Thyroid hyperplasia seen in rats at all dose levels of OBBP and the top two dose levels of DBDPO was quite possibly a physiological response to competition between bromine and iodine in the thyroid gland. Such a response is not unexpected at high dose levels with materials containing bromine in quantities as great as in OBBP and DBDPO.

DBDPO did not cause a teratogenic response in fetuses of rats administered 1000, 100, or 10 mg of DBDPO/kg-day on gestation days 6–15. No indications of toxicity, adverse effects on food consumption, or body or liver weights were observed in the maternal rats at any of the dose levels of DBDPO. At the high dose level, the bromine content of the maternal livers was increased. The bromine content of fetal livers, was, however, unaffected by the administration of DBDPO to maternal rats at any dose level included in this study.

The no-effect level in this teratology study was 100 mg of DBDPO/kg-day. The number of resorptions occurring at the two lower levels of DBDPO was statistically greater than the controls. However, as this effect did not occur at the high dose level, it was probably due to chance rather than treatment.

Fetal toxicity in the form of subcutaneous edema was noted in fetuses of dams at the high dose level of DBDPO. The only other effect noted was delayed ossification of normally developed bones of the fetal skull occurring similarly at the high dose level.

Aftosmis et al. (7) have reported that OBBP administered in diets of pregnant rats caused a teratogenic response, gastroschisis, in some of the fetuses of dams on diets containing 0.1 and 1.0% of OBBP. The bromine content was increased in the liver and fat of the OBBP treated maternal rats and also in the whole fetus.

The reproductivity of rats chronically maintained on diets containing DBDPO was unaffected at the highest dose level administered, 100 mg/kg-day. Inclusion of DBDPO in the diet had no detrimental effect on the resultant offspring and no cytogenetic effects were seen in parental or weanling bone marrow cells.

The data from the 30-day dietary feeding study and the teratology study indicate that the degree of hazard that exists from long-term exposure to DBDPO is significantly less than to OBBP. The ^{14}C metabolism study, reproduction study, and the special studies on absorption, accumulation, and elimination, which were subsequently conducted, offer additional substantiation for this observation.

The results of the metabolism study show that the half-life for the disappearance of ^{14}C activity from the body of DBDPO-treated rats was less than 24 hr. The disappearance of ^{14}C activity from the body of OBBP-treated rats was biphasic. The half-life of the first phase was less than 24 hr, the second phase greater than 16 days. The principal route of excretion for both experimental materials was via the feces. No appreciable ^{14}C activity (less than 1%) was found in either urine or expired air. There were no sex-related differences in the way these materials were excreted by the rats.

Examination of the various tissues for radioactivity at 1, 3, and 16 days following administration of OBBP and DBDPO labeled with ^{14}C revealed that absorption had occurred with both materials. The levels of ^{14}C activity in the various tisues of the OBBP-treated rats were greater than those found in the corresponding tissues of DBDPO-treated rats. The ^{14}C activity readily cleared from the tissues of the DBDPO-treated rats, whereas on day 16, the last day of the study, ^{14}C activity persisted in the adrenal tissue, skin, adopose tissue, and heart of the OBBP-treated rats.

The results of the metabolism study further suggest that DBDPO does not have the potential of OBBP to bioaccumulate. The special tissue accumulation study revealed that after 180 days, there was no accumulation of OBBP or DBDPO in serum, kidney, skeletal muscle, or testes of rats on diets providing 0.1 mg/kg-day. The sites of deposition were the liver and adipose tissue. The bromine content increased rapidly in both these tissues of the OBBP-treated rats. The bromine content of the livers of the DBDPO-treated rats reached a plateau after 30 days. The bromine concentration in the livers of the DBDPO-treated rats sacrificed after 180 days on tests were not statistically different from those of the controls. Analysis of the data on the bromine content in adipose tissue of DBDPO treated rats over a 12-month

period revealed no accumulation in this tissue.

The special study on the elimination of bromine from various tissues of rats maintained for 90 days on diets providing 1.0 mg of OBBP or DBDPO/kg-day revealed high levels of bromine in the liver and adipose tissue of the OBBP-treated rats and low levels in the DBDPO-treated rats. Bromine was not eliminated from adipose tissue of the OBBP-treated rats and only partially eliminated from the liver of these rats after 90 days on recovery.

The low level of bromine in adipose tissue of the DBDPO-treated rats remained unaffected during the 90 days on recovery diets. The bromine concenration in the liver of these rats was not significantly higher than in the control livers after the first 10 days' recovery.

The in-depth toxicological investigation on DBDPO is continuing to be pursued by The Dow Chemical Company.

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