

7/11/81

*Environmental Biology and Chemistry Branch
National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina 27709*

As interest in the biologic effects of environmental pollutants grows it becomes increasingly evident that a number of these chemicals can cause alterations in the immune function of an exposed subject. Of the chemicals of environmental concern that have been shown to induce immune alterations 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) has been investigated most extensively.

TCDD is a chlorinated hydrocarbon found to be a contaminant in biocides (trichlorophenol), herbicides (2,4,5-T), and products from chemical sensitizing processes in which polychlorinated phenols are used.¹ This compound has previously been shown to induce atrophy of thymus and peripheral lymph nodes of rats, mice, and guinea pigs.²⁻⁴ In addition, TCDD has been shown to suppress thymic-dependent immune function^{4,6} and resistance to bacterial infection.⁷ The suppression of cell-mediated immune functions includes suppression of mitogen responsiveness,^{4,6} suppression of skin graft rejection⁵ and suppression of delayed hypersensitivity responses.^{8,9} Suppression of these T-cell-dependent immune functions appears to occur without helper cell function being affected.¹

Previous studies utilizing rats to investigate the effects of developmental TCDD exposure on immune functions have utilized Fischer rats.^{5,6} Recently it was reported that the Fischer rat is a poor immunologic responder.⁹ In order to investigate the effects of developmental TCDD exposure on a strain of rat with a good immunologic response, experiments performed previously in Fischer rats⁶ were repeated in Fischer/Wistar rats.⁹

To accomplish this, female Fischer rats bred to male Wistar rats were randomly distributed into three dosage groups. (1) The control group was dosed with corn oil (0.1 ml/100 g body weight) on gestational day 18. At parturition, the neonates were cross-fostered among these females; all litters were standardized at eight pups per litter. Nursing rats were also dosed with corn oil (0.1 ml/100 g body weight) on postnatal days 0, 7 and 14. (2) Females in the postnatal group were allowed to litter, and neonates were cross-fostered among these females; litters were standardized at

504

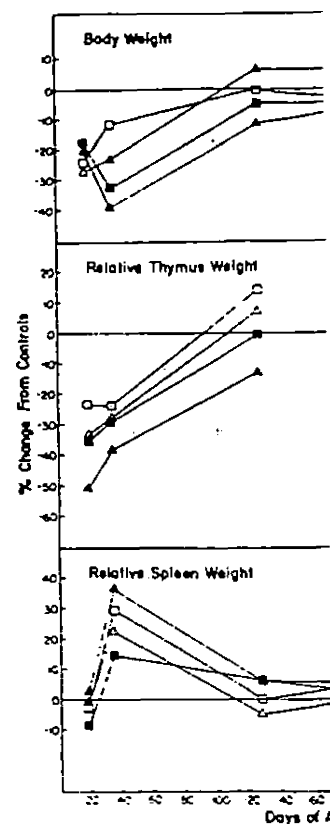


FIGURE 1. Effect of developmental TCDD expo weights. □, female animals exposed to TCDD postna 0, 7 and 14; ■, female animals exposed to TCDD post female animals exposed to TCDD pre- and postnatal gestational day 18 and on days 0, 7 and 14; and ▲, mice dosing as above. Relative thymus and spleen weights.

Significant Variations from Control	
Age in Days	$p < 0.05$
18	
body wt.	□
rel. thy. wt.	□
rel. spleen wt.	All N.S.*
35	
body wt.	□
rel. thy. wt.	■
rel. spleen wt.	△
128	
body wt.	
rel. thy. wt.	
rel. spleen wt.	All N.S.*
270	
body wt.	All N.S.*
rel. thy. wt.	All N.S.*
rel. spleen wt.	All N.S.*

^a NS indicates nonsignificant differences from control.

EFFECTS OF P-DIOXIN (TCDD) ON IMMUNE FUNCTIONS

J. I. Luster

Immunology Branch
Health Sciences
Carolina 27709

Environmental pollutants grow it becomes
clear that chemicals can cause alterations in the
functions of environmental concern
such as 2,3,7,8-tetrachlorodibenzo-
p-dioxin.

It may be a contaminant in biocides
which leaches from chemical sensitizing
agents.¹ This compound has previously
been shown to suppress thymic-dependent
immune function.² The suppression of cell-
mediated immunity of mitogen responsiveness,³⁻⁶
and the induction of delayed hypersensitivity
immune functions appears to occur

EXPOSURE ON IMMUNE FUNCTION IN RATS

The effects of developmental TCDD
on rats.^{7,8} Recently it was reported
that in order to investigate the
effects of rat with a good immunologic
Fischer rats⁹ were repeated in

male Wistar rats were randomly
divided into two groups. One group was dosed with corn oil
At parturition, the neonates were
standardized at eight pups per
litter (0.1 ml/100 g body weight) on
natal day 14. The neonates were allowed to litter.
At weaning, litters were standardized at

Roberts University, Tulsa, Oklahoma

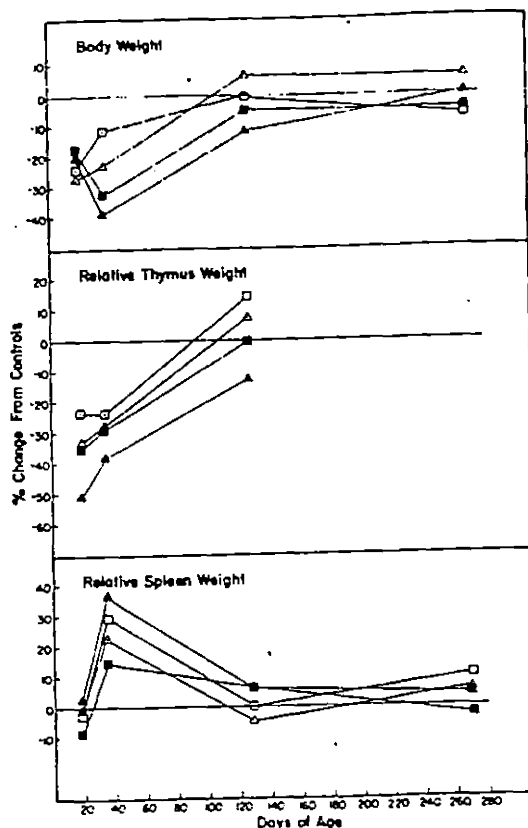


FIGURE 1. Effect of developmental TCDD exposure on body weight and selected organ weights. $\square$, female animals exposed to TCDD postnatally via maternal dosing ($5 \mu\text{g}/\text{kg}$) on day 0, 7 and 14; $\blacksquare$, male animals exposed to TCDD postnatally via maternal dosing as above; $\triangle$, female animals exposed to TCDD pre- and postnatally via maternal dosing ($5 \mu\text{g}/\text{kg}$) on gestational day 18 and on days 0, 7 and 14; and $\blacktriangle$, male animals exposed to TCDD via maternal dosing as above. Relative thymus and spleen weights represent organ-to-body-weight ratios.

Age in Days	Significant Variations from Control $p < 0.05$	$p < 0.01$
18		$\square, \blacksquare, \triangle, \blacktriangle$
body wt.		$\blacksquare, \triangle, \blacktriangle$
rel. thy. wt.	$\square$	
rel. spleen wt.	All N.S.*	
35		$\blacksquare, \triangle, \blacktriangle$
body wt.	$\square$	$\square, \triangle, \blacktriangle$
rel. thy. wt.	$\blacksquare$	$\square, \triangle$
rel. spleen wt.	$\triangle$	
128		$\blacktriangle$
body wt.		$\blacktriangle$
rel. thy. wt.	All N.S.*	
rel. spleen wt.	All N.S.*	
270		
body wt.	All N.S.*	
rel. thy. wt.	All N.S.*	
rel. spleen wt.	All N.S.*	

*N.S. indicates nonsignificant differences from control

eight pups per litter. Nursing rats were dosed with 5 $\mu\text{g}/\text{kg}$ TCDD (Dow Chemical Co., Midland, Michigan, lot 851-144-11, more than 99% pure) on postnatal days 0, 7, and 14. (3) Females in the prenatal-postnatal group were dosed with 5 $\mu\text{g}/\text{kg}$ TCDD on gestational day 18. At parturition the neonates were cross-fostered to untreated females and the litters were standardized at eight pups per litter. The nursing females received doses of TCDD (5 $\mu\text{g}/\text{kg}$) on postnatal days 0, 7, and 14. All rat pups were weaned at 25 days of age. These animals were utilized to investigate the effects of TCDD exposure on various parameters of immune function.

FIGURE 1 illustrates the effect of TCDD exposure on body weight, relative thymus weight, and relative spleen weight. Developmental TCDD exposure resulted in depressed body and relative thymus weights in males and females of both treatment groups at 18 and 35 days of age. By 128 days of age body weights and relative thymus weights were still slightly suppressed in the prenatally treated males whereas values were normal or above normal for the other treated animals. This is similar to results previously obtained in Fischer rats.⁶ At 35 days of age the relative spleen weights in both groups of TCDD-exposed animals were greater than those of nonexposed animals. This ratio reflects the change in body weight, as actual spleen weights did not vary significantly between the groups.

In vitro mitogen stimulation of lymphocyte cultures was performed using spleen and thymus cells from TCDD-exposed and nonexposed animals as previously described.⁶ Results of mitogen stimulation were evaluated by calculating stimulation indices (counts per minute incorporated into stimulated cultures divided by counts per minute incorporated into nonstimulated cultures) and relating the indices of stimulation of cultures from TCDD-exposed animals to the indices of stimulation of cultures from nonexposed animals. FIGURE 2 illustrates the effect of developmental TCDD exposure on mitogen responsiveness of splenic and thymic lymphocytes. Prenatal and postnatal and postnatal only exposure to TCDD suppressed the response of splenic and thymic lymphocytes to stimulation by the mitogens phytohemagglutinin (PHA) and Concanavalin A (Con A). The response of splenic lymphocytes had returned to normal by 270 days of age. Thymic cultures were not performed at 270 days of age because of extreme thymic involution at this time. There was a trend towards recovery of mitogen responsiveness in thymic lymphocytes over the time course studied.

Delayed hypersensitivity reactions (DHR) were utilized as an *in vivo* assessment of cell-mediated immune function. The DHRs were performed according to the radiometric assay method of Leford.¹⁰ The effect of developmental TCDD exposure on delayed hypersensitivity responsiveness is illustrated in FIGURE 3. TCDD exposure resulted in a suppression of delayed hypersensitivity responses at 35 and 133 days of age. By 270 days of age the response of exposed animals had returned to normal.

The final assay of immune function investigated in the Fischer/Wistar animals was antibody production. Animals were immunized with primary and secondary injections of bovine gamma globulin (BGG) in complete Freund's adjuvant at various ages. Serum was obtained from the immunized animals at approximately weekly intervals for 5 weeks and antibodies to BGG assayed for by passive hemagglutination reactions. FIGURE 4 illustrates the antibody responses obtained in these animals. Developmental TCDD exposure had no apparent effect on antibody responses. These results indicate that at least one T-cell function, that of helper cell function, is spared from TCDD suppression, as BGG is a T-dependent antigen.

ALTERATIONS IN LYMPHOCYTE HOMING PATTERNS AS A RESULT OF DEVELOPMENTAL TCDD EXPOSURE

Inbred Fischer rats were exposed to TCDD as described for the prenatal-postnatal exposure group described above. At 45 days of age these animals were utilized to

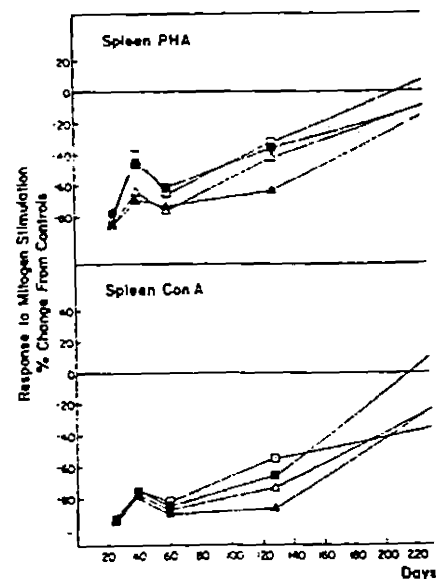


FIGURE 2. Effect of developmental TCDD exposure on mitogen stimulation. Legend as in FIGURE 1.

Age in Days	Significant Variation $p < 0.05$
25	
Spleen PHA	
Con A	
Thymus PHA	□
Con A	□, *
35	
Spleen PHA	
Con A	
Thymus PHA	□
Con A	
59	
Spleen PHA	
Con A	
Thymus PHA	□
Con A	□
128	
Spleen PHA	
Con A	
Thymus PHA	□, *
Con A	
270	
Spleen PHA	All N.
Con A	All N.

* N.S. indicates nonsignificant difference from controls.

5 µg/kg TCDD (Dow Chemical, 99% pure) on postnatal days 0, 7, and 14. The pups were cross-fostered to untreated pups per litter. The nursing females were dosed with 5 µg/kg TCDD on days 0, 7, and 14. All rat pups were utilized to investigate the effects of TCDD on immune function.

On body weight, relative thymus weight, and spleen weight, TCDD exposure resulted in lower values in males and females of both treatment groups compared to untreated males whereas values were similar in untreated females. This is similar to results obtained in other studies where the relative spleen weights in TCDD-treated animals were greater than those of nonexposed animals, as actual spleen weights did not differ.

Assessment of immune function was performed using spleen and thymus lymphocytes from unexposed animals as previously described. Cultures were stimulated by calculating stimulation indices divided by counts per minute and relating the indices of stimulation of cultures to the indices of stimulation of cultures of unexposed lymphocytes. Prenatal and postnatal TCDD exposure did not affect the response of splenic and thymic lymphocytes to phytohemagglutinin (PHA) and concanavalin A (Con A). Lymphocytes had returned to normal by 270 days of age because of the trend towards recovery of mitogen response course studied.

TCDD was utilized as an *in vivo* assessment of immune function. These were performed according to the methods described in FIGURE 3. TCDD exposure did not affect lymphocyte responses at 35 and 128 days of age. By 270 days of age, lymphocyte responses had returned to normal. This was observed in the Fischer/Wistar animals treated with primary and secondary Freund's adjuvant at various intervals and at approximately weekly intervals for by passive hemagglutination. The responses obtained in these animals were similar to those obtained in the Fischer/Wistar animals. The effect on antibody responses. These results of helper cell function, is spared from the effects of TCDD exposure.

IMMUNE PATTERNS AS A FUNCTION OF TCDD EXPOSURE

As described for the prenatal-postnatal TCDD exposure, these animals were utilized to

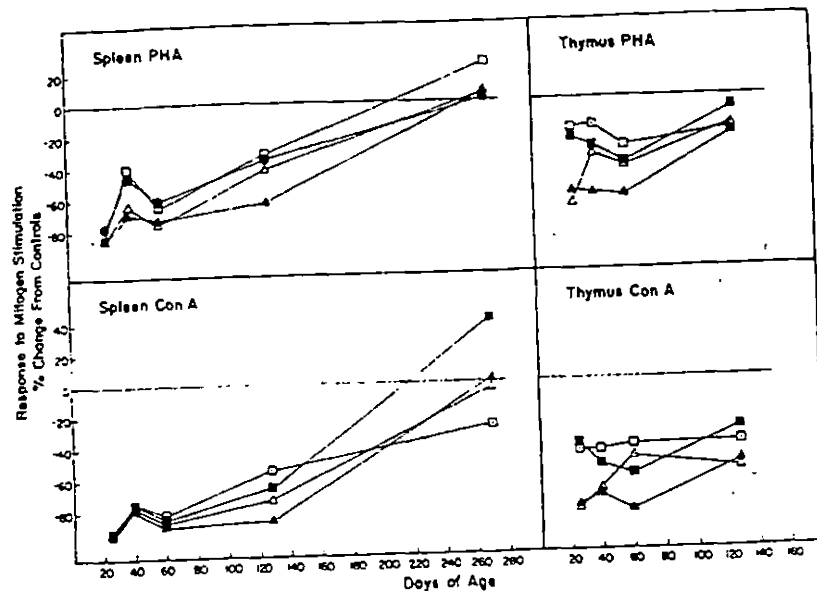


FIGURE 2. Effect of developmental TCDD exposure on *in vitro* lymphocyte responsiveness to mitogen stimulation. Legend as in FIGURE 1.

Age in Days	Significant Variations from Control $p < 0.05$	$p < 0.01$
24		□, ■, △, ▲
Spleen PHA		□, ■, △, ▲
Con A	□	■, △, ▲
Thymus PHA	□, ■	△, ▲
Con A		
35		
Spleen PHA		■, △, ▲
Con A	□	□, ■, △, ▲
Thymus PHA		□, ■, △, ▲
Con A		■, △, ▲
59		
Spleen PHA		□, ■, △, ▲
Con A		□, ■, △, ▲
Thymus PHA		■, △, ▲
Con A		■, △, ▲
128		
Spleen PHA		■, △, ▲
Con A		□, ■, △, ▲
Thymus PHA		△
Con A	□, ▲	□, ■, △, ▲
270		
Spleen PHA	All N.S.*	
Con A	All N.S.*	

*N.S. indicates nonsignificant difference from control.

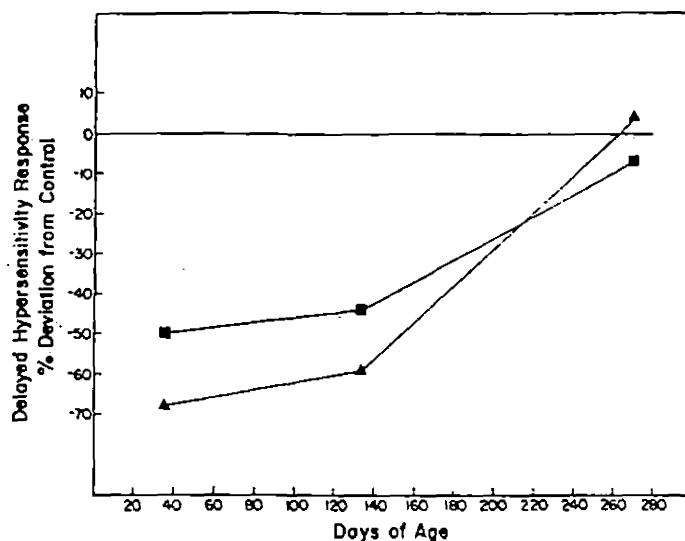


FIGURE 3. Effect of developmental TCDD exposure on delayed hypersensitivity responsiveness. ■, animals exposed to TCDD postnatally through maternal dosing ($5 \mu\text{g/kg}$) on days 0, 7 and 14; and ▲, animals exposed to TCDD pre- and postnatally by maternal dosing ($5 \mu\text{g/kg}$) on gestational day 18 and on days 0, 7, and 14. At 35 and 133 days of age both TCDD dosage groups responded at a level significantly lower than nonexposed animals ($p < 0.01$). At 270 days of age there was no significant difference between responses of exposed and nonexposed animals.

investigate the effects of TCDD exposure on lymphocyte homing patterns. Lymphocytes from spleen, thymus, bone marrow and lymph node were isolated from TCDD exposed and nonexposed animals, labeled with ^{51}Cr , and injected in TCDD-exposed and nonexposed recipients. TCDD exposure altered the homing of exposed spleen cells to the thymus in nonexposed animals. In addition, TCDD exposure altered the pattern of homing of nonexposed thymus cells in exposed animals and the pattern of homing of exposed thymus cells in nonexposed animals.

CONCLUSIONS

The highly toxic chlorinated hydrocarbon TCDD appears to be equally as immunosuppressive in a strain of rat that is a good immunologic responder (Fischer/Wistar) as it is in the Fischer rat,^{4,9,8} which is a poor immunologic responder. The immunosuppression induced by developmental exposure to TCDD in the Fischer/Wistar rat is long lasting, as has previously been shown to be true in the Fischer rat.⁹ The exposed animals do recover from the induced immunosuppression by 270 days of age, however.

At present the mechanism of induction of immunosuppression by TCDD is unknown. The results of these experiments indicate that whatever the mechanism the effects are reversible.

In an effort to understand more fully the types of defects in immune function induced by exposure to TCDD, studies on the effects of TCDD exposure on homing

patterns of lymphocytes were performed. TCDD significantly increases the thymic lymphocyte population. When injected into nonexposed recipients, TCDD-exposed lymphocytes decreased homing to spleen and thymus recipients. At the same time thymic lymphocytes decreased homing to thymus in nonexposed recipients.

While there is controversy about the effects of TCDD on homing patterns of lymphocytes, the results of these TCDD-induced modification of non-

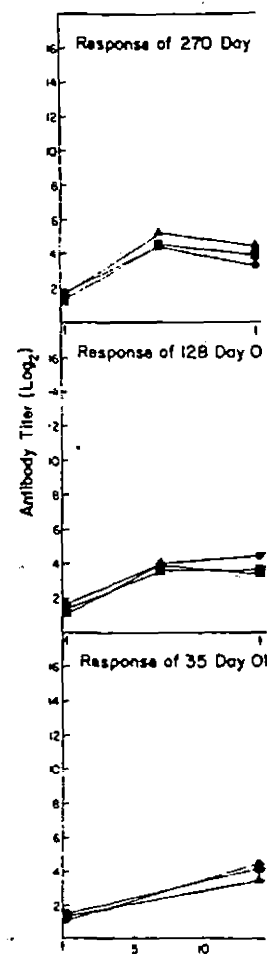


FIGURE 4. Effect of developmental TCDD exposure on antibody titer. ●, nonexposed animals; ■, animals exposed to TCDD through maternal dosing ($5 \mu\text{g/kg}$) on days 0, 7, and 14; or through maternal dosing ($5 \mu\text{g/kg}$) on gestational day 18 and on days 0, 7, and 14. Significant differences were observed between exposed and nonexposed animals at 35 and 128 days of age.

patterns of lymphocytes were performed. It was found that TCDD exposure significantly increases the thymic uptake of spleen cells from TCDD-exposed animals injected into nonexposed recipients. Thymic cells from non exposed animals showed decreased homing to spleen and increased homing to thymus in TCDD exposed recipients. At the same time thymic lymphocytes from TCDD exposed donors showed decreased homing to thymus in non-exposed recipients.

While there is controversy about the role of cell surface markers in control of homing patterns of lymphocytes,¹² the data obtained here are consistent with TCDD-induced modification of normal cell-surface markers. This modification could

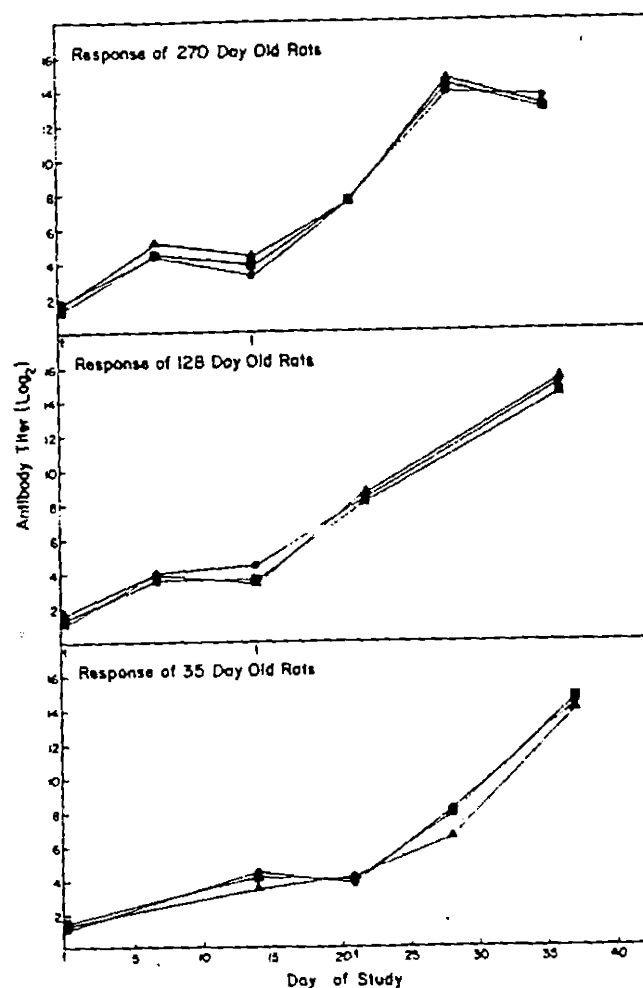
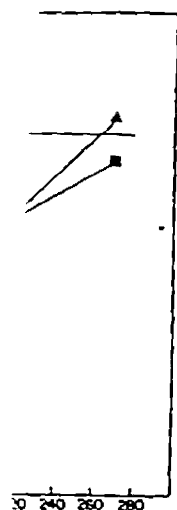


FIGURE 4. Effect of developmental TCDD exposure on antibody response to bovine gamma globulin. ●, nonexposed animals; ■, animals exposed to TCDD postnatally by means of maternal dosing (5 μ g/kg) on days 0, 7, and 14; and ▲, animals exposed to TCDD pre- and postnatally by means of maternal dosing (5 μ g/kg) on gestational day 18 and on days 0, 7, and 14. No significant differences were observed between nonexposed and TCDD-exposed animals.

ices



hypersensitivity responsive-
osing (5 μ g/kg) on days 0, 7
maternal dosing (5 μ g/kg) on
of age both TCDD dosage
nals ($p < 0.01$). At 270 days
of exposed and nonexposed

homing patterns. Lympho-
were isolated from TCDD
njected in TCDD-exposed
ring of exposed spleen cells
posure altered the pattern
and the pattern of homing of

appears to be equally as
d immunologic responder
or immunologic responder.
posure to TCDD in the
on shown to be true in the
need immunosuppression by

osuppression by TCDD is
whatever the mechanism the

ffects in immune function
TCDD exposure on homing

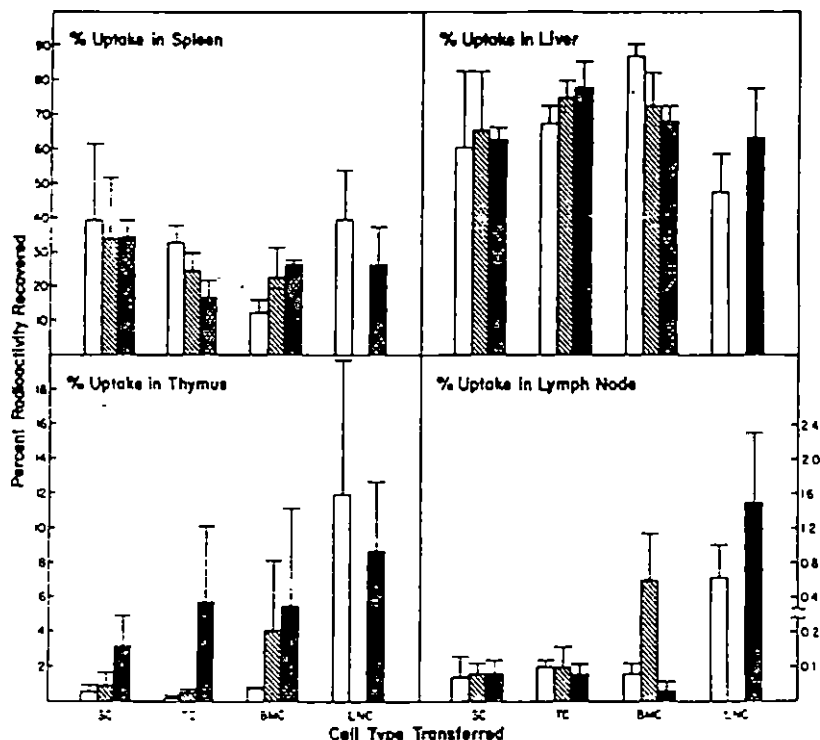


FIGURE 5. Effect of developmental TCDD exposure on lymphocyte homing patterns. The open bars represent cells from nonexposed animals injected into nonexposed animals, the shaded bars represent cells from nonexposed animals injected into TCDD-exposed animals, and the crosshatched bars represent cells from TCDD-exposed animals injected into nonexposed animals. Significant differences occurred in splenic uptake of thymus cells. Nonexposed cells homed to nonexposed spleen in greater numbers than to exposed spleen ($p = 0.06$) and in greater numbers than exposed cells homed to nonexposed spleen ($p < 0.01$). In addition, nonexposed cells homed to exposed spleen in greater numbers than exposed cells homed to nonexposed spleen ($p = 0.054$). TCDD-exposed bone marrow cells homed to nonexposed spleen in greater numbers than nonexposed bone marrow cells migrated to nonexposed spleen ($p < 0.01$). TCDD-exposed spleen cells homed to nonexposed thymus in greater numbers than nonexposed spleen cells homed to nonexposed or exposed thymus ($p < 0.01$). TCDD-exposed thymus cells homed to nonexposed thymus in greater numbers than nonexposed thymus cells homed to nonexposed thymus ($p < 0.01$). Nonexposed bone marrow cells home to nonexposed liver in greater numbers than exposed bone marrow cells homed to nonexposed liver ($p < 0.01$). All other comparisons were nonsignificant.

be accomplished by at least two mechanisms: (1) a TCDD-induced change in cellular metabolism resulting in an altered cell membrane; or (2) alteration of the cell membrane by insertion of TCDD into the membrane. In any case, TCDD exposure appears to alter homing markers in the spleen and thymus, as well as on the lymphocyte, as evidenced by alteration of homing patterns of normal thymic and splenic lymphocytes when injected into TCDD-exposed recipients.

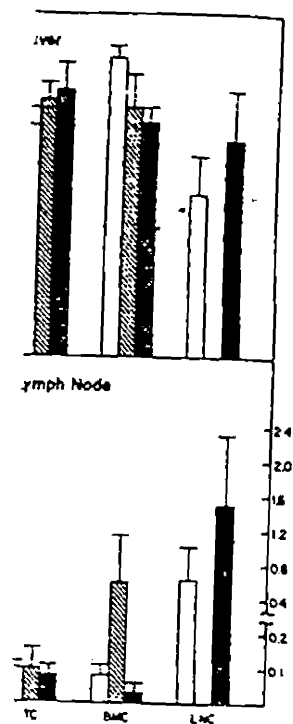
SUMM

The effects of TCDD exposure on postnatal developmental period were investigated. Exposed rats. Fetal and neonatal rats were exposed (5 $\mu\text{g}/\text{Kg}$) on day 18 of gestation and on days 0, 7, and 14 of postnatal life only (group 2). Another group of neonatal rats were exposed on days 0, 7, and 14 of postnatal life only (group 1). Parameters of cell-mediated immune function were investigated. TCDD suppressed cell-mediated immune function by 270 day of age.

A group of inbred Fischer rats was exposed above. At 45 days of age these animals were found that TCDD exposure alters homing patterns when adoptively transferred to nonexposed animals did not home no recipients.

REFERE

1. MOORE, J. A. 1973. Perspective on chlorinated hydrocarbons. *Health Perspect.* 5: 1.
2. GUPTA, B. N., J. G. VOS, J. A. MOORE, J. A. MOORE, J. A. MOORE. 1974. Effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on the immune system of rats. *Health Perspect.* 5: 125-140.
3. HARRIS, M. W., J. A. MOORE, J. G. VOS & J. A. MOORE. 1974. TCDD in laboratory animals. *Environ. Health Perspect.* 5: 125-140.
4. VOS, J. G., J. A. MOORE & J. G. ZINK. 1974. *p*-dioxin on the immune system of rats. *Health Perspect.* 5: 149-162.
5. VOS, J. G. & J. A. MOORE. 1974. Suppression of maternal treatment with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Immunol.* 47: 777-794.
6. FAITH, R. E. & J. A. MOORE. 1977. Impaired exposure of the developing immune system to TCDD. *J. Toxicol. Environ. Health* 3: 1-10.
7. THOMPSON, J. E., R. E. FAITH, E. E. MOORE. 1977. Susceptibility to bacterial infection as a result of *p*-dioxin. *Infect. Immun.* 12: 1319-1324.
8. FAITH, R. E., M. I. LUSTER & J. A. MOORE. 1977. Function and delayed hypersensitivity response in rats. *J. Immunol.* 128: 19-29.
9. TADA, N., K. ITAKURA & M. AIZAWA. 1977. Inbred rats. *J. Immunogenet.* 1: 265.
10. LEFFORD, J. J. 1974. The measurement of allergic response. *Allergy Appl. Immunol.* 47: 570-585.
11. MORSE, H. C., III & ASOFKY, R. 1974. Homing patterns and graft-versus-host reaction. *Immunol.* 11: 19-29.
12. SCHLESINGER, M. 1976. Cell surface receptors. *Comm. Biochem. Physiol.* 5: 775-793.



lymphocyte homing patterns. The nonexposed animals, the shaded TCDD-exposed animals, and the injected into nonexposed animals. Nonexposed cells homed to = 0.06) and in greater numbers addition, nonexposed cells homed to nonexposed spleen ($p = < 0.01$). TCDD-exposed spleen nonexposed spleen cells homed to thymus cells homed to nonexposed thymus ($p < 0.01$) in greater numbers than exposed. All other comparisons were

TCDD-induced change in cellular or (2) alteration of the cell in any case, TCDD exposure thymus, as well as on the terms of normal thymic and recipients

SUMMARY

The effects of TCDD exposure on parameters of immune function during the developmental period were investigated. Exposures were performed in Fischer/Wistar rats. Fetal and neonatal rats were exposed to TCDD through maternal dosing (5µg/Kg) on day 18 of gestation and on days 0, 7, and 14 of postnatal life (group 1). Another group of neonatal rats were exposed to TCDD through maternal dosing on days 0, 7, and 14 of postnatal life only (group 2). Body weights and relative thymus weights were found to be suppressed up to 135 days of age in group 1 but only up to 35 days of age in group 2. Parameters of cell-mediated and humoral immune function were investigated. TCDD suppressed cell-mediated immune function without affecting humoral immune function. TCDD-exposed animals had recovered normal cell-mediated immune function by 270 days of age.

A group of inbred Fischer rats was exposed to TCDD as described for group 1 above. At 45 days of age these animals were utilized in lymphocyte homing studies. It was found that TCDD exposure alters homing patterns of lymphocytes from exposed animals when adoptively transferred to untreated animals. In addition, lymphocytes from nonexposed animals did not home normally when injected into TCDD-exposed recipients.

REFERENCES

1. MOORE, J. A. 1973. Perspective on chlorinated dibenzodioxins and dibenzofurans. *Environ. Health Perspect.* 5: 1.
2. GUPTA, B. N., J. G. VOS, J. A. MOORE, J. G. ZINKL & B. C. BULLOCK. 1973. Pathologic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin in laboratory animals. *Environ. Health Perspect.* 5: 125-140.
3. HARRIS, M. W., J. A. MOORE, J. G. VOS & B. N. GUPTA. 1973. General biological effects of TCDD in laboratory animals. *Environ. Health Perspect.* 5: 101-109.
4. VOS, J. G., J. A. MOORE & J. G. ZINKL. 1973. Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin on the immune system of laboratory animals. *Environ. Health Perspect.* 5: 149-162.
5. VOS, J. G. & J. A. MOORE. 1974. Suppression of cellular immunity in rats and mice by maternal treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Int. Arch. Allergy Appl. Immunol.* 47: 777-794.
6. FAITH, R. E. & J. A. MOORE. 1977. Impairment of thymus-dependent immune function by exposure of the developing immune system to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). *J. Toxicol. Environ. Health* 3: 451-464.
7. THIGPEN, J. E., R. E. FAITH, E. E. MCCONNELL & J. A. MOORE. 1975. Increased susceptibility to bacterial infection as a sequela of exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Infect. Immun.* 12: 1319-1324.
8. FAITH, R. E., M. I. LUSTER & J. A. MOORE. 1978. Chemical separation of helper cell function and delayed hypersensitivity responses. *Cell. Immunol.* In press.
9. TADA, N., K. ITAKURA & M. AIZAWA. 1974. Genetic control of the antibody response in inbred rats. *J. Immunogenet.* 1: 265.
10. LEFFORD, J. J. 1974. The measurement of tuberculin hypersensitivity in rats. *Int. Arch. Allergy Appl. Immunol.* 47: 570-585.
11. MORSE, H. C., III & ASHESKY, R. 1974. *In vivo* effects of antithymocyte serum on the homing patterns and graft-versus-host reactivity of murine splenic lymphocytes. *Cell. Immunol.* 11: 19-29.
12. SCHLESINGER, M. 1976. Cell surface receptors and lymphocyte migration. *Immunol. Comm.* 5: 775-793.