Renal Tubular Tumors and Atypical Hyperplasias in B6C3F1 Mice Exposed to Lead Acetate during Gestation and Lactation Occur with Minimal Chronic Nephropathy

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ABSTRACT

Lead is a high-priority hazardous substance in humans and a renal carcinogen in adult rodents. This study assessed the carcinogenic potential and toxicity of gestational and lactational lead exposure in (C57BL/6NCr × C3H/HeN)F1 (hereafter called B6C3F1) mice. Effects of a renal tumor promoter (barbital sodium (BB)) on lead-initiated lesions were also studied. Pregnant female C57BL/6NCr mice (10–15/group) previously bred with C3H/HeN males were given lead acetate (0, 500, 750 and 1000 ppm lead) ad libitum in their drinking water, starting on gestation day 12 and continuing to 4 weeks postpartum. Offspring were then weaned and divided into same-sex groups of 23–25 and observed for a maximum of 112 weeks. Other groups received lead and then continuous BB (500 ppm) ad libitum in their drinking water from weaning onward. In control male offspring (0 lead/0 BB), renal proliferative lesions (RPLs); defined as atypical tubular hyperplasia or tumor) occurred rarely (1 lesion-bearing mouse/23 mice examined, 4%) and did not include tumors. RPLs increased in a dose-related fashion with lead exposure (500 lead/0 BB, 4/25, 16%; 750 lead/0 BB, 6/25, 24%; 1000 lead/0 BB, 12/25, 48%) in male offspring and were often multiple. All lead-treated groups had renal tumors, including carcinoma, but these were most common at the highest dose (1000 lead/0 BB, 5/25). Lead-induced renal tumors arose in the absence of the extensive chronic nephropathy and lead inclusion bodies typically seen with lead carcinogenesis in rodents exposed chronically as adults. Postnatal BB exposure had no effect on RPL incidence (e.g., 1000 lead/500 BB, 8/25, 32%). Lead-treated female offspring also developed RPLs, including adenoma and carcinoma, but at a much lower rate than males. Thus, short-term lead exposure during the gestational/lactational period has carcinogenic potential in the mouse kidney.

INTRODUCTION

Each year, the Agency for Toxic Substance and Disease Registry and Environmental Protection Agency are required by law to develop a list of the environmental chemicals that pose the greatest hazard to the population of the United States. For many years, lead has been considered to be the toxicant that poses the greatest risk.

Lead and inorganic lead compounds are rated by the IARC as possible human carcinogens (category 2B) based primarily on rodent data (1, 2). However, as is the case with other carcinogenic or potentially carcinogenic metals, the mechanism of oncogenic action of lead is only poorly defined (3). In rats or mice, chronic exposure to high-dose p.o. lead induces renal adenocarcinomas and adenomas in a dose-related fashion (4–8). Carcinogenically effective levels of lead in the diet generally range from 1,000 to 10,000 ppm lead (1.0–0.1%) and require a 12–24-month period of continuous feeding to be active (1, 5, 6, 8). However, lead is also a very effective nephrotoxicant, inducing a continuum of dose- and duration-related effects, beginning with an acute reversible nephropathy characterized by intranuclear inclusion bodies and, with continued lead exposure, progressing to a chronic nephropathy characterized by interstitial fibrosis and cystic hyperplasia (9–12). Renal carcinogenesis in rodents has not been reported at doses of lead below those which produce significant levels of chronic nephropathy (10, 11). On the basis of the observation that lead-induced tumors in the rodent kidney have only occurred under conditions of extensive renal injury, it has been proposed that severe renal toxicity is the etiological basis of these tumors (13–15). The association of lead-induced tumors with the chronic nephropathic effects of the metal has led to the conclusion that lead carcinogenesis occurs largely through nongenotoxic mechanisms, possibly involving genetic errors provoked during increased mitogenesis stemming from the necessity for continuous proliferative cellular repair (11, 16). However, the results of studies directly examining the genotoxic effects of lead have often been contradictory (1, 13–15, 17), the precise mechanism(s) of lead carcinogenicity must be considered as largely unknown.

Very little is known about the carcinogenic potential of perinatal lead exposure. However, lead moves freely across the placenta from the mother to the fetus (18, 19) and is actually mobilized from maternal stores during pregnancy (20–22). lead is also found in breast milk (23) and can be readily transferred through the milk to suckling animals (24, 25). Addition of milk to the diet will increase tissue deposition of lead at several sites, including the bone and kidney (26). In fact, lead has many recognized transplacental toxic effects (11, 18, 19), including embryotoxicity and delayed neuropathic effects. The perinatal period is often a time of high sensitivity to various toxic metals, including lead (11). In this regard, recent studies in rodents indicate that several metals or metal compounds may be active transplacental carcinogens or cocarcinogens, resulting in tumor formation in the offspring of mothers treated during pregnancy. For instance, platinum compounds can induce preneoplastic and neoplastic changes in the skin, kidney, or lung after transplacental exposure in mice (27) or in the kidney or liver in transplacentally exposed rats (28). Similarly, transplacental nickel exposure initiates kidney tumors and induces a high incidence of pituitary tumors in rats (29). Nickel is recognized as a human carcinogen while platinum compounds are probably carcinogenic in humans (3).

Therefore, in the present study we assessed the carcinogenic potential of combined transplacental and translactational lead exposure in mice. Since the kidney is a recognized target of lead carcinogenesis in rodents (3), the effects of a known renal tumor promoter (BB); Refs. 30 and 31) on any lead-induced renal lesions were also studied.

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3 The abbreviations used are: BB, barbital sodium; RPL, renal proliferative lesion.

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TUMORS, ATYPICAL HYPERPLASIAS IN MICE EXPOSED TO LEAD ACETATE

MATERIALS AND METHODS

Chemicals. Lead acetate, as lead\(\left(C_{2}H_{3}O_{2}\right)_{2} \cdot 3 H_{2}O\), was obtained from Fisher Scientific (Rockville, MD), and barbital, as the sodium salt, was obtained from Sigma Chemical Company (St. Louis, MO).

Animals and Treatments. Animal care was provided in accordance with the procedures outlined in the "Guide for Care and Use of Laboratory Animals" (NIH Publication 86–23). A total of 60 female C57BL/6NCr mice were obtained from the Animal Production Area, National Cancer Institute-Frederick Cancer & Research Development Center, Division of Cancer Treatment Animal Program (Frederick, MD). Female mice were bred with male C3H/HeNCr(MTV), also from the Animal Production Area, National Cancer Institute-Frederick Cancer & Research Development Center, to obtain B6C3F1 offspring. Mice were housed in a standard barrier facility at a temperature of 68–72°F, with a relative humidity of 50 ± 5% and a 12-h light/dark cycle. A basal diet (NIH-31 Open Formula, 6% modified; Teklad Standard Diets, Madison, WI) and water (unmodified or modified as below) were provided ad libitum. Individual body weights, survival, and clinical signs were recorded throughout the experiment and at necropsy.

The experimental design is shown in Fig. 1. Primigravid female C57BL/6NCr mice (10–15/group) previously bred with C3H/HeNCr males were given lead acetate (0, 500, 750, and 1000 ppm lead) ad libitum in their drinking water, starting on gestation day 12 and continuing to 4 weeks postpartum. Offspring were then weaned and divided into same-sex groups of 25 and observed for a total of 112 weeks. Other groups of offspring received lead (0, 500, 750, and 1000 ppm lead) as described above and then received continuous BB (500 ppm) ad libitum in their drinking water from weaning onward. Assuming a mature mouse would weigh in the range of 25 g and would consume an average of 5 ml drinking water/day (32), these drinking water levels of lead (0, 500, 750, and 1000 ppm) would translate to approximate doses of 0, 100, 150, and 200 mg lead/kg/day.

For p.o treatment, lead acetate was mixed in deionized water to the level of lead desired and then acidified with acetic acid to pH 4.5. Control groups received acidified water only. BB was administered in acidified drinking water.

Pathology. Necropsies were performed on all moribund animals, animals found dead, or on mice at terminal sacrifice. The following tissues were taken and processed using standard techniques for histological analysis: brain, pituitary, gonads (ovaries or testes), liver, kidneys, lung, a sampling of bone, and all grossly abnormal tissues. Longitudinal sections of each kidney were used. Tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, and processed using standard techniques for histological analysis: brain, pituitary, gonads (ovaries or testes), liver, kidneys, lung, a sampling of bone, and all grossly abnormal tissues. Longitudinal sections of each kidney were used. Tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at 5 µm, and stained with hematoxylin and eosin for histological analysis. Renal preneoplastic and neoplastic lesions were classified into three categories: atypical tubular hyperplasia, tubular adenoma, and adenocarcinoma. Atypical tubular hyperplastic foci were composed of single tubules with in situ abnormal changes and dysplastic basophilic cells with one to three cells lining the tubule but with no disruption of the basement membrane. Adenomas were well differentiated, small to large (1–10 mm), and compressed adjacent parenchyma. Most adenomas were solid, some had lipid droplets, and one was papillary. Adenocarcinomas were invasive, less-differentiated lesions composed of irregularly arranged cells forming either solid or tubular structures with mitotic figures and central necrosis. RPLs for statistical purposes were defined as combined atypical hyperplasia, adenoma, and adenocarcinoma, and lesions of tubular carcinoma.
considered to represent stages within a progressive continuum of putative preneoplastic, premalignant, and malignant lesions (7, 33, 34). Acid-fast stain was used to determine the presence of lead intranuclear inclusions in renal preneoplastic, premalignant, and malignant lesions (7, 33, 34). Acid-fast stain was suspected as a primary target site for lead carcinogenesis. To expedite reporting, lesions in tissues other than kidney will be described elsewhere. In all cases, a two-sided probability level of \( P < 0.05 \) was considered to indicate a significant difference. In a pairwise comparison of lesion incidence, Fisher’s exact test was used. To define treatment-related trends in renal proliferative lesions, the Cochran-Armitage test for trend was used. Body weight data were considered highly significant positive trends with the dose for lead alone (\( P = 0.0006 \)) or for lead plus BB (\( P = 0.022 \)).

### RESULTS

In the present study, we assessed the carcinogenic potential of combined transplacental and translactational lead exposure in B6C3F1 mice. The lead exposures did not affect average litter size [500 ppm lead, 7.0 ± 2.2 pups/litter (mean ± SE), \( n = 10–15 \) litters; 750 ppm lead, 7.9 ± 3.1; 1000 ppm lead, 8.0 ± 2.9] compared to control (7.9 ± 2.2). The lead levels also did not affect the growth of treated offspring (Fig. 2). Body weights during the study were similar for all same-sex groups regardless of lead treatment. Likewise, survival was not adversely affected by these levels and durations of lead exposure (Fig. 3). BB did not modify weight gain (Fig. 2) or survival (data not shown).

The carcinogenic effects of combined transplacental and translactational exposure to lead acetate in the kidney of male B6C3F1 mice are shown in Table 1. Lead alone caused a dose-related increase in RPLs (includes atypical hyperplasia, adenoma, and carcinoma) in male mice. BB did not elevate this rate further. Renal tumor incidence was significantly increased at the highest dose of lead (1000 ppm) regardless of additional BB treatment. Tumors included both renal tubular cell adenoma and adenocarcinoma. A total of four renal tubular adenocarcinomas was observed in lead-exposed male mice. Tumors, both adenomas and adenocarcinomas, were often quite large and could be grossly observed (Fig. 4). Renal tumors were not observed in control male mice while atypical hyperplasia was only seen in one male mouse (4%).

The effects of combined gestational and lactational exposure to lead acetate in the kidney of female B6C3F1 mice are shown in Table 2. Lead alone caused a significant dose-related trend in RPLs in female mice. With BB treatment, this trend was lost. A total of one renal tubular adenocarcinoma and two renal tubular cell adenomas were observed in treated females. Neither renal tumors nor atypical hyperplasias were observed in control female mice.

Of the total of five renal adenocarcinomas that occurred in the lead-treated mice, all were from animals derived from different litters. Morphological types of renal lesions induced in mice exposed to lead acetate during the perinatal period are shown in Figs. 5 (adenomas) and 6 (carcinomas and atypical tubular hyperplasias). Renal tubular adenomas of both the solid (Fig. 5, A and B) and papillary (Fig. 5, C and D) type occurred with lead exposure. Renal tubular carcinomas induced by lead exposure included both trabecular (Fig. 6A) and undifferentiated (Fig. 6B) types. It is noteworthy that the kidney tissue adjacent to tumors appeared to be normal in most of the cases, or had only mild degrees of aging nephropathy similar to that of control mice. Atypical tubular hyperplastic foci were composed of

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**Table 1 Renal tubular cell tumors and potential preneoplastic lesions in male B6C3F1 mice exposed to lead acetate during the perinatal period**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of mice reviewed</th>
<th>Renal tubular cell adenoma</th>
<th>Renal tubular cell carcinoma</th>
<th>Renal tubular cell atypical hyperplasia(^b)</th>
<th>Total RPLs(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>23</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>lead, 500 ppm</td>
<td>25</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>lead, 750 ppm</td>
<td>25</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>lead, 1000 ppm</td>
<td>25</td>
<td>5(^d)</td>
<td>0</td>
<td>7(^d)</td>
<td>12 (46%)</td>
</tr>
<tr>
<td>BB alone</td>
<td>24</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>lead, 500 ppm + BB</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>lead, 750 ppm + BB</td>
<td>25</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>lead, 1000 ppm + BB</td>
<td>25</td>
<td>5(^d)</td>
<td>1</td>
<td>2</td>
<td>8 (32%)</td>
</tr>
</tbody>
</table>

\(^a\) See Figure 1 for treatment details.

\(^b\) In the absence of tumor.

\(^c\) RPLs including adenoma, carcinoma, and atypical hyperplasia. Total RPLs showed highly significant positive trends with the dose for lead alone (\( P = 0.0006 \)) or for lead plus BB (\( P = 0.022 \)).

\(^d\) Significant difference from appropriate control.
single tubules with *in situ* abnormal changes and dysplastic basophilic cells (Fig. 6C). Lead-treated mice rarely had cytomegalic tubular cells but never with intranuclear inclusions (Fig. 6D). In fact, no acid-fast inclusions were observed. Cystic tubules, seen frequently in overt lead-induced nephropathy, were found occasionally in controls and were slightly more common in lead-exposed males. However, overall, renal tumors develop in the absence of evidence of significant concurrent lead-induced chronic nephrotoxicity, which is typically characterized by intranuclear inclusion bodies, interstitial fibrosis, and cystic hyperplasia. Thus, the evidence indicates renal tumor histogenesis in this case was associated with minimal, if any, lead nephropathy.

**DISCUSSION**

Lead is considered to be the toxicant that poses the greatest risk to the population of the United States and is a known carcinogen in adult rodents (1, 2, 4–8). Although previously it was thought that lead acts largely or exclusively through nongenotoxic mechanisms involving lead-induced chronic nephrotoxicity, which is typically characterized by intranuclear inclusion bodies, interstitial fibrosis, and cystic hyperplasia (9–12). Prior to this report, renal carcinogenesis induced by lead in rodents had not been reported in the absence of significant levels of chronic lead-induced nephropathy. The association of lead-induced tumors with the chronic nephropathic effects of the metal led to the conclusion that lead carcinogenesis occurs due to chronic severe toxicity (13–15) and possibly through nongenotoxic mechanisms involving errors induced during increased mitogenesis resulting from continuous proliferative cellular repair (11, 16). Although this may be an important factor in some cases, in the present study renal tumors developed essentially in the absence of any evidence of concurrent lead-induced chronic nephrotoxicity. Thus, clearly the evidence in this case indicates that renal tumor histogenesis was not associated with chronic nephropathy and suggests that alternative mechanisms must be considered.

Since carcinogenic effects occurred long after cessation of lead exposure in this study, the renal tumorigenesis is probably not dependent on the continuous presence of lead in the kidney. In this regard, results of a study defining lead metabolism after translacational exposure in rats indicated that lead levels, although elevated at weaning, return to control levels in the kidney within a relatively short period (4 months; Ref. 24). In combination with the present results, in which offspring had received no additional lead treatment for up to 108 weeks, this indicates that persistent changes had occurred during the translacational or translactational lead exposure period. Although stimulation of cell proliferation may be a contributor to carcinogenesis in various tissues, including kidney, there are many examples indicating it does not necessarily lead to enhancement of carcinogenesis (35). In fact, although chronic toxic lesions associated with increases in cell turnover have been, on occasion, observed in target organs of “nongenotoxic” carcinogens, many more organ-specific nongenotoxic toxins are not carcinogens in rodent carcinogenesis experiments (35).

The precise oncogenic mechanism of lead is not known. Lead and lead compounds have often been presumed to be without genotoxic potential, since *in vitro* studies in both mammalian and bacterial systems have generally failed to show that lead has significant direct mutagenic activity (15). However, lead acetate can induce *in vitro* transformation in a dose-related fashion and can be mutagenic at relatively nontoxic concentrations in mammalian cells (15, 17). Lead can also be mutagenic at the *Escherichia coli* gpt locus transfected to mammalian cells (36). More recent evidence also indicates that lead compounds may be genotoxic by indirect mechanisms in *in vitro* systems. For instance, although lead acetate alone does not induce DNA strand breaks, mutations at the hypoxanthine phosphoribosyltransferase locus, or sister chromatid exchanges in *in vitro* systems, lead inhibits closing of UV-induced DNA strand breaks and enhances UV-induced mutation and sister chromatid exchanges (37, 38), indicating an effect on DNA repair. Such potentially genotoxic mechanisms for lead-induced cellular transformation *in vitro* would be consistent with the present results *in vivo*, indicating that a persistent change had occurred during translacational and translactational lead exposure.

Lead was most active as a renal carcinogen in male mice in the present study. Given the fact that the occurrence of spontaneous renal neoplasia in B6C3F1 mice is exceedingly rare (39–42), the incidence of nearly 50% renal proliferative lesions in male mice exposed translacationally and translactationally to lead is highly significant. The

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**Table 2 Renal tubular cell tumors and potential preneoplastic lesions in female B6C3F1 mice exposed to lead acetate during the perinatal period**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of mice reviewed</th>
<th>Renal tubular cell adenoma</th>
<th>Renal tubular cell carcinoma</th>
<th>Renal tubular cell atypical hyperplasia</th>
<th>Total RPLs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>lead, 500 ppm</td>
<td>24</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>lead, 750 ppm</td>
<td>25</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>lead, 1000 ppm</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>BB alone</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>lead, 500 ppm + BB</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>lead, 750 ppm + BB</td>
<td>25</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>lead, 1000 ppm + BB</td>
<td>25</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2 (8%)</td>
</tr>
</tbody>
</table>

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**Notes:**

- See Figure 1 for treatment details.
- In the absence of tumor.
- RPLs including adenoma, carcinoma, and atypical hyperplasia. Total RPLs showed a significant positive trend with the dose for lead alone (*P* = 0.017) but not for lead plus BB (*P* = 0.094).
female mice in the present study also showed some evidence of sensitivity to lead-induced neoplastic transformation in the kidney. The incidence of renal tumors is often higher in male animals or humans (11, 31, 43–45), indicating that gender-dependent variables play an important role. One such aspect that has been proposed as a gender-specific sensitivity factor in renal carcinogenesis is α2-microglobulin (46). Some chemicals will induce the accumulation of the α2-microglobulin complex in the male rat kidney, and this accumulation is thought to initiate a sequence of events that involves persistent cell death and proliferative replacement and may lead to renal tubule tumor formation (46). It has been proposed that lead interaction with α2-microglobulin alters normal renal gene expression and plays an important role in the association of high-dose lead and renal cancer (10, 47). However, it appears that the sequence of events leading to renal neoplasia with α2-microglobulin is associated in a highly specific manner only with globulin produced by the male rat and not with that produced by female rats, male mice, or female mice (46). Thus, the finding of renal tumors in both male and female mice in the absence of evidence of chronic renal toxicity (including hyaline droplets) in the present study largely negates a possible or potential role for this particular protein in lead-induced renal tumor formation in the mouse.

The finding of transplacental potential for lead carcinogenicity in mice should be seen as the basis for several critical future studies. The transplacental/translactational carcinogenicity should be confirmed in another species, such as the rat. Furthermore, the genotoxic potential

Fig. 5. Morphological type of renal lesions induced in mice exposed to lead acetate during the perinatal period: adenomas. Mice were treated with lead or lead plus BB as shown in Fig. 1. A, solid tubular adenoma (A) in otherwise normal kidney (N) without nephropathy (lead, 1000 ppm; BB, 500 ppm; H & E, ×75). B, solid tubular adenoma in kidney (lead, 1000 ppm; BB, 500 ppm; H & E, ×150). C, tubular adenoma, papillary type (P), in otherwise normal area of kidney (N) without nephropathy (lead, 1000 ppm; BB, 500 ppm; H & E, ×75). D, tubular adenoma showing papillary structure and lack of nephropathy in adjacent parenchyma (lead, 1000 ppm; BB, 500 ppm; H & E, ×150).
of lead should be studied in detail in vivo by duplicating the treatment protocol of the present study and analyzing renal tissue at or near term or near weaning to define the molecular events possibly associated with lead initiation by analysis of various parameters of genotoxicity. Since our study with lead had both transplacental and translactational exposure elements, the contribution to carcinogenesis of each exposure route should be separately defined in chronic testing. It should be kept in mind, however, that the combination of both transplacental and translactational exposures in rodent models would be the most realistic in terms of actual human exposure and, since lead is well transported to the offspring by either means (18–20, 23–25), creating such a distinction may prove somewhat arbitrary and artificial.

In the present study, the addition of BB had little or no effect on renal carcinogenesis. BB can be nephrotoxic and is a strong promoter of renal carcinogenesis in males (30, 31). It is, however, a very weak promoter of renal carcinogenesis initiated with transplacental N-nitrosoethylurea in B10.A mice (30). In the present study, BB failed to exhibit any promoting effect on renal carcinogenesis initiated by transplacental/translactational lead. The lack of promoting effect of BB on renal carcinogenesis in this study may be related to the dose of BB, the strain of mice used (B6C3F1), and/or the nature of the carcinogen used to initiate carcinogenesis (lead). In fact, there is evidence that promoting agents can select for different types (populations) of initiated cells (48, 49), and BB may simply not promote the...
population initiated by lead. Further study will be required to define this apparent lack of effect.

Lead exposure during the perinatal period in B6C3F1 mice was associated with renal carcinogenesis. This occurred in the absence of significant chronic lead-induced nephrotoxicity, indicating that lead-induced renal cellular proliferation as a chronic toxic response was not responsible or absolutely required for tumor formation. Renal tumors developed long after a relatively short-term exposure to transplacental and transplacental lead, and tumors occurred largely in the absence of chronic site-specific toxicity. This could be an important finding in evaluating potential human risk.

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