NO SIGNIFICANT RISK LEVELS (NSRLS) FOR THE PROPOSITION 65 CARCINOGENS LEAD AND LEAD COMPOUNDS (ORAL)

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SUMMARY OF FINDINGS

This document provides a basis for the estimation of cancer risk from exposure to lead. Carcinogenic potencies were estimated from oral studies of the carcinogenicity of lead compounds. These estimated potencies were based upon the administered doses of lead; in some cases, it was necessary to calculate lead dose based upon the lead content of the administered compounds. The uncertainty associated with the estimation of cancer risk from exposure to specific forms of lead is recognized. Based on the findings from the administration of different lead compounds by different routes to experimental animals, it is clear that the lead component of these compounds is responsible for renal carcinogenicity. In the absence of clear evidence to the contrary, it will be assumed that the lead content of lead compounds is responsible for the carcinogenicity of these compounds. Uncertainty also exists regarding the relationship of chemical form to cancer potency, particularly with respect to the influence of form on oral absorption. Absorption data are not available for all lead compounds for which there is potential human exposure, and physicochemical properties (such as water solubility) have not proven to be reliable predictors of absorption. Since the estimation of risk in this assessment is based upon studies conducted with relatively highly absorbed lead compounds, the cancer potencies derived here are expected to be larger (on lead bases) than those for lead compounds which are less well absorbed.

There is some indication of potentially increased sensitivity of the developing fetus and neonate to the carcinogenic effects of lead. However, this possibility has not been formally addressed in this analysis. It is suggested that the potential increased risk of *in utero* and perinatal exposures can be considered explicitly when circumstances warrant it. Risks from *in utero* and perinatal lead exposure may be underestimated by the potency presented here.

Multiple studies in which rats exposed to lead compounds over a wide range of doses developed renal tumors were identified as suitable for the estimation of cancer potency. The cancer potency estimate presented below was derived based upon a geometric mean of five studies in rats conducted in the lower dose range. The potency estimate and no significant risk level (NSRL) associated with a lifetime cancer risk of 10^{-5} is as follows:

Compound	Basis of Estimate			Human Cancer Potency (Oral)	No Significant Risk Level
	Species	Route	Site		
Lead	Rat	Oral	Kidney	0.047 $(mg/kg\text{-}day)^{-1}$	15 µg/day

Based upon their molecular weights, corresponding oral route NSRLs for other lead compounds are:

Compound	Human Cancer Potency (Oral)	No Significant Risk Level
Lead acetate	0.030 $(mg/kg\text{-}day)^{-1}$	23 µg/day
Lead phosphate	0.012 $(mg/kg\text{-}day)^{-1}$	58 µg/day
Lead subacetate	0.017 $(mg/kg\text{-}day)^{-1}$	41 µg/day

1. INTRODUCTION

Under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65, California Health and Safety Code Section 25249.5 *et seq.*), "lead and lead compounds" have been listed as chemicals known to the State to cause cancer, effective October 1, 1992. Prior to that, several specific lead compounds had been listed including lead acetate on January 1, 1988, lead phosphate on April 1, 1988, and lead subacetate on October 1, 1989.

1.1. Physicochemical Properties and Occurrence

Elemental lead is a naturally occurring metal in the earth's crust. Lead and lead compounds have numerous commercial and industrial uses including the production of batteries and ammunition and as additives to certain paints, ceramic glazes, and caulking (ATSDR, 1993). Table 1 below provides some basic information on lead and several lead compounds.

Table 1. Select lead compounds, molecular weight, CAS Registry number, molecular formula, and solubility in water (Humphreys, 1991; ATSDR, 1993).

Chemical	Mol. Wt.	CAS Reg. No.	Formula	Solubility in Water
Lead	207.2	7439-92-1	Pb	Insoluble
Lead acetate	325.3	301-04-2	$C_4H_6O_4Pb$	Very soluble
Lead carbonate	267.2	598-63-0	CO_3Pb	Insoluble
Lead chloride	278.1	7758-95-4	$PbCl_2$	Slightly soluble
Lead oxide	223.2	1317-36-8	OPb	Insoluble
Lead nitrate	331.2	10099-74-8	N_2O_6Pb	Very soluble
Lead phosphate	811.5	7446-27-7	$O_8P_2Pb_3$	Insoluble
Lead subacetate	566.5	1335-32-6	$C_4H_8O_6Pb_2$	Very soluble
Lead sulfide	239.3	1314-87-0	PbS	Insoluble

2. CARCINOGENIC EFFECTS

The purpose of this report is to derive cancer potency estimates for lead and lead compounds. For this reason, only data directly pertaining to cancer potency estimation will be discussed in detail.

2.1. Humans

The California Air Resources Board's Toxic Air Contaminant Program (OEHHA, 1997) found some evidence of carcinogenicity from studies of people occupationally exposed to lead. CARB (1997) did not find the evidence convincing due to lack of control for confounders and to the simultaneous exposure in some studies to known human carcinogens. Nonetheless, evidence of lead carcinogenesis in humans has continued to evolve (Vainio, 1997) since the IARC (1980), U.S. EPA (1986), U.S. EPA (1989a), U.S. EPA (1989b), and ATSDR (1990) reviews. A follow-up epidemiological study by Steenland *et al.* (1992), a meta-analysis of occupational studies of lead exposure and cancer by Fu and Boffetta (1995), and several case-control or cohort studies (Anttila *et al.*, 1995; Kandiloros *et al.*, 1997; Anttila *et al.*, 1996; Lundström *et al.*, 1997) suggest a relationship between lead and human cancer. Sites reported with increased risk include the lung, kidney, gastrointestinal tract, and brain.

However, the lack of detail in reporting limit the usefulness of these studies for quantitative risk assessment of cancer from exposure to lead and lead compounds. Should more detailed information be obtained on some of the better studies from study authors, the dose-response relationship should be re-evaluated.

2.2. Animals

Because of limited reporting of details in the available human studies, the animal cancer bioassays are relied upon to derive quantitative estimates of cancer potency.

2.3. Available Data Sets

In selecting studies as bases for potency estimation, those conducted using routes of exposure corresponding to likely human exposures are normally considered. In the case of developing an oral risk specific intake level for lead and lead compounds, only studies conducted by the oral route, including several feed studies and a drinking water study, were considered. The following sections describe these studies. Tumors were assessed for all major organ systems in the experimental animals in most of the studies. Where limited examinations appear to have occurred, a statement to this effect has been added to the description.

<u>Feed Studies with Lead Acetate</u>

Zawirska and Medras, 1968

Groups of 94 male and 32 female Wistar rats were fed diet containing lead acetate such that the dose received was 3 mg/day for two months, then 4 mg/day for 16 months. A control group of 32 rats was included. Renal tumors were reported in 58 of 94 male rats and 14 of 32 female rats. [Summary as cited in HSDB, 2000 and IARC, 1980]

Zawirska and Medras, 1972

Groups of male and female Wistar rats (47/sex/group), aged 215 days, were treated orally in feed with lead acetate at 3 mg/day for varying lengths of time, ranging from 60 days to lifetime. Twenty-six rats (13/sex) received lead acetate for more than one year, including seven killed after 504 days on the lead diet (four male, three female), and 19 treated until their natural deaths (nine male, ten female). Among those animals treated for life, renal adenomas (4), brain gliomas (2), lung adenomas (2), hypophyseal adenomas (2), thyroid adenomas (2), parathyroid adenomas (2), and prostate adenomas (2) developed. The sex of the rats developing tumors was not reported. No malignant tumors were reported among lead acetate treated animals and no "neoplastic hyperplasia" was observed in 31 male and 31 female control rats.

Azar et al., 1973

Groups of male and female rats (strain not stated) were fed diet containing lead acetate for two years. Two studies were conducted separated in their start date by several months, one with lower doses of 0, 10, 50, 100 and 500 ppm lead as lead acetate (n = 50/sex/group, plus 100 controls) and another with higher doses of 0, 1000, and 2000 ppm lead as lead acetate (n = 20/sex/group). Renal tumors were significantly increased in the 500, 1000, and 2000 ppm dose groups in male rats and in the 2000 ppm dose group in female rats relative to their respective control groups (see Table 2). The tumors were reported to be primarily adenomas derived from the tubular epithelium and the contribution of carcinomas to the incidence was not stated. The most notable effect on survival was among male rats exposed to 2000 ppm lead acetate having 80% mortality. No increases in tumor incidence were reported at other sites. This study was extremely limited in its reporting of experimental detail and results concerning carcinogenic endpoints.

Table 2. Kidney tumors in rats fed diet containing lead acetate (Azar *et al.*, 1973).

Pb Concentration in Feed (ppm)		Kidney Tumor Incidence		Mortality (%)	
Added	Measured	Male	Female	Male	Female
0	5	0/100	0/50	37	34
10	18	0/50	0/50	36	30
50	62	0/50	0/50	36	28
100	141	0/50	0/50	36	28
500	548	5/50*	0/50	52	36
0	3	0/20	0/20	50	35
1000	1130	10/20*	0/20	50	50
2000	2102	16/20*	7/20*	80	35

* Significant increase in incidence relative to controls by Fisher's exact test ($p < 0.05$).

Nogueira, 1987

Groups of 10 or 12 male Wistar rats were fed diet containing 0, 0.5, or 1.0% lead acetate (by weight) for 24 weeks. Tissues examined were limited to kidneys, liver, esophagus, and lungs. No renal tumors were observed in the rats treated at the lower dose (0/12), but basophilic (2/10) and chromophobic (7/10) renal tumors were observed in the higher dose group (total renal tumors: 9/10). While a control group was explicitly mentioned in the experimental design, the study failed to report the incidence of renal tumors in this group.

Feed Studies with Lead Subacetate

Boyland et al., 1962

Groups of 20 male Wistar rats were fed diet containing either 1% lead acetate (by weight) or 0.5% sedormid (allylisopropylacetylcarbamide) for one year. No control group was reported. Among the rats administered lead acetate, renal tumors developed in 15 of 16 rats surviving to 331 days, which was the time the first renal tumor was reported. All but one of the renal tumors were carcinomas. No tumors were reported at sites other than the kidney, although it is unclear from the study reporting the extent to which other tissues were examined. The lack of an appropriate control group precludes the use of this study in the quantitative risk assessment of lead compounds.

Van Esch et al., 1962

Groups of Wistar rats (12-15/sex) were fed diet containing lead subacetate at concentrations of 0, 0.1, and 1% by weight. The low- and high-dose groups each had its own control group. The low-dose study was conducted for 29 months while the high-dose study was conducted for 24 months. Survival was slightly lower in low-dose controls relative to treated groups, while

survival was lower for the high-dose treated group relative to its control group. Kidney tumors (reported as combined adenomas and carcinomas) were significantly increased in males relative to their control groups (5/16 low-dose *vs.* 0/14 control; 6/13 high-dose *vs.* 0/13 control) and in females relative to their control groups (6/16 low-dose *vs.* 0/15 control; 7/11 high-dose *vs.* 0/13 control). Differences were statistically significant with all p-values less than 0.03 by Fisher's exact test. No increases in tumor incidence were reported at other sites.

Mao and Molnar, 1967

Groups of male Wistar rats (40 treated; 20 control) were fed diet containing lead subacetate at 1% by weight for up to 690 days. The incidence of renal tumors was significantly increased among treated animals (31/40 treated *vs.* 1/20 control; $p < 10^{-7}$, by Fisher's exact test). As reported in the study, many animals in both the lead treated and control groups were sacrificed at different times before the end of the study, with 13 animals sacrificed between 213 and 593 days of treatment and the remaining 27 dying spontaneously between 162 and 677 days of treatment. The reported experimental detail does not allow one to draw conclusions as to whether the sacrifice occurred because of morbidity. This limits the study's reliability for purposes of quantitative risk assessment. It is also unclear the extent to which tissues other than the kidney were examined.

Van Esch and Kroes, 1969

Groups of Swiss mice (25/sex/dose) were fed diet containing lead subacetate at 0, 0.1, and 1.0% for two years. The lead subacetate levels administered to the high-dose group were reduced to 0.5% at 92 days for males and at 114 days for females, due to toxicity. Significant and high mortality was observed in both male and female mice in the high-dose groups. Among control animals, no kidney tumors were observed. Among low-dose male mice, two kidney adenomas and four carcinomas were observed (including one clear cell carcinoma). Among low-dose female mice, one kidney adenoma was observed. Among high-dose animals, only a single kidney carcinoma was observed in a female mouse, although poor survival severely limited the ability to detect carcinogenic effects in the high-dose groups (only two male and five female mice survived to one year). Only low-dose male mice showed a statistically significant increase in kidney tumors based upon an estimate of at-risk mice surviving to one year from the study's survival curve (6/20 *versus* 0/19, $p = 0.01$ by Fisher's exact test). No significant increases in tumor incidence were reported at other sites.

Groups of golden hamsters (22-24/sex/dose) were fed diet containing lead subacetate at 0, 0.1, and 0.5% for two years. Survival was reduced in the high-dose group, and slightly reduced in the low-dose group. No significant increase in tumor incidence was reported at any site.

Oyasu et al., 1970

Seventeen male CD rats were fed diet containing 1.0% lead subacetate for 46.6 weeks. Of these, 13 developed tumors of the renal cortex and two developed brain gliomas. One brain glioma was reported among 325 control rats. The incidence of renal tumors among control animals was not reported. The increase in gliomas is statistically significant ($p = 0.0068$, by Fisher's exact test).

Kasprzak et al., 1985

Groups of 30 male Sprague-Dawley rats were fed diet containing 0 or 1.0% lead subacetate for 18 months. Renal tumors were significantly increased among treated animals (13/29 treated *vs.* 0/30 control; $p < 10^{-4}$ by Fisher's exact test). The reported tumors were primarily adenomas (11/29). Treatment with lead did not appear to affect survival. Only kidney, liver, and tissues with gross lesions were examined histologically.

Drinking Water Studies with Lead Acetate

Koller et al., 1985

Sixteen male Sprague-Dawley rats were exposed to drinking water containing lead (as lead acetate) at a concentration of 2600 ppm for 76 weeks. A control group of 10 male rats was included in the study. Among treated rats, renal tubule carcinomas developed in 13 of 16 animals, with three tumors observed at 72 weeks and the balance at the end of the study. No renal tumors were observed among control rats, although three of these rats died of pneumonia before the end of the study. The authors' report of the effective size of the control group as seven rats suggests these animals died before the appearance of the first renal tumor in the lead acetate exposed group. No increases in tumor incidence were reported at other sites.

Waalkes et al., 1995

Waalkes et al. examined the effects of transplacental and translactational exposure to lead on the development of tumors in B6C3F1 mice. Female C57BL/6NCr mice (10-15/group) mated with male C3H/HeNCr mice were exposed to lead acetate in drinking water from gestational day 12 through four weeks postpartum. The concentrations of lead in the drinking water were 0, 500, 750, and 1000 ppm, which the authors calculated as doses of 0, 100, 150, and 200 mg/kg-day based upon a female mouse body weight of 25 g and an average daily water consumption of 5 ml/day. Twenty-five offspring mice of each sex were then weaned and observed for a total of 112 weeks. No effects on average litter size, growth of offspring, body weight, or survival were observed.

Among male mice perinatally exposed to lead, renal tubular cell carcinomas developed in 0/23, 1/25, 1/25, and 0/25 mice in increasing dose groups. Renal tubular adenomas developed in 0/23, 0/25, 0/25, and 5/25 mice in increasing dose groups. Combined renal tumor incidences were 0/23, 1/25, 1/25, and 5/25. The increase in renal tubular adenomas was statistically significant in the highest dose group. Each of the tumors developed in a mouse from a different litter. Among female mice, one renal tubular adenoma developed in a mouse in the mid-dose group. No other renal tumors were observed. According to the authors, "renal tumors developed 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."

Fowler and Lipsky, 1999

Male Fischer rats (80/group) were exposed to lead acetate in drinking water at concentrations of 0, 50, 250, and 1000 ppm for up to two years. Interim sacrifices of 5-10 animals per group were conducted at six, 12, and 18 months. The incidences of renal tumors among the rats are

presented in Table 3. No renal tumors were reported at the six or 12 month interim sacrifices, however, a significant increase in renal adenomas was observed at 1000 ppm in the rats sacrificed at 18 months. Statistically significant increases in renal adenomas and renal carcinomas were observed in the 1000 ppm dose group, both among animals killed at terminal sacrifice (24 months) and among unscheduled mortalities occurring between 18 months and the terminal sacrifice. Among all rats surviving to 18 months (combined unscheduled mortalities, 18-month and terminal sacrifices) the incidences of adenomas and carcinomas were increased in both the 250 and 1000 ppm dose groups. The number of animals examined for tumors in the control and 50 ppm groups at terminal sacrifices and among unscheduled mortalities, while not explicitly stated in the document, was inferred from the number examined for other nephrotoxic endpoints.

Table 3. Kidney tumors in male rats treated with drinking water containing lead acetate (Fowler and Lipsky, 1999).

Dose group	Renal tumors							
	18 mo. (interim)		24 mo. (terminal)		18-24 mo. (unsched)		Total**	
(ppm)	Adeno.	Carc.	Adeno.	Carc.	Adeno.	Carc.	Adeno.	Carc.
0	0/5	0/5	0/35	0/35	0/15	0/15	0/55	0/55
50	0/6	0/6	0/25	0/25	0/11	0/11	0/42	0/42
250	1/6	0/6	3/23	3/23	1/23	2/23	5/52 *	5/52 *
1000	6/8 *	2/8	8/12 *	11/12 *	8/21 *	11/21 *	22/41 *	24/41 *

* Significant increase in incidence relative to controls by Fisher's exact test ($p < 0.05$).

** Total tumor incidence from animals examined between 18 and 24 months.

Studies with Other Lead Compounds

Schroeder et al., 1970

Groups of 52 male Long-Evans rats were administered drinking water containing zero or 25 ppm lead nitrate. The authors also reported that the diet contained 0.2 mg Pb/kg. No increase in tumors was reported, although this finding was based upon the assessment of visible tumors at necropsy. Total tumors were also not increased relative to control animals (7/43 treated *vs*. 10/50 control).

2.4. Methodology Used to Derive Cancer Potency

2.4.1 Mathematical Model for Carcinogenesis

For regulatory purposes, the lifetime probability of dying with a tumor (p) induced by an average daily dose (d) is often assumed to be modeled by the "multistage" polynomial (CDHS, 1985; U.S. EPA, 1987; Anderson and U.S. EPA, 1983):

$$p(d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + \cdots + q_j d^j)]$$

with constraints

$$q_i \geq 0 \text{ for all i.}$$

The q_i are parameters of the model which are taken to be constants and are estimated from the data. The parameter q_0 represents the background lifetime incidence of the tumor. q_1, or some upper bound, is often called the cancer potency, since for small doses it is the ratio of excess lifetime cancer risk to the average daily dose received. For the present discussion, cancer potency will be defined as q_1^*, the upper 95% confidence bound on q_1 (CDHS, 1985), estimated by maximum likelihood techniques. When dose is expressed in units mg/kg-d, the parameters q_1 and q_1^* are given in units $(\text{mg/kg-d})^{-1}$. Details of the estimation procedure are given in Crump (1981) and Crump *et al.* (1977).

Dose rates (in mg/kg-day) were not presented in the reports of lead carcinogenicity, rather lead exposure was usually reported in these studies as percent or parts per million in feed or drinking water. Data on parameters needed for the calculation of the dose rates (*e.g.*, average body weights, food consumption rates) were likewise not presented in most of the studies' findings. Fowler and Lipsky (1999) presented average body weights for both lead-treated and control rats at six, 12, 18, and 24 months, with 400 g as a reasonable average over the course of the experiment. Drinking water consumption values were reported to be 18 ml/day for the initial six months of the experiment and were reported not to change significantly during the six and 12 month and the 12 to 18 month intervals, although values were reported to be "slightly higher" for the six to 12 interval. During the final interval of 18 to 24 months, water consumption was reported to be increased in the low-dose group (69 ml/day) compared to the mid-dose group (54 ml/day) and the high-dose group (48 ml/day). Since measured consumption rates were incompletely reported, a reasonable default water consumption rate of 25 ml/day was used for the calculation of the dose rates in the Fowler and Lipsky study. Kasprzak *et al.* (1985) showed the growth curve for the male Sprague-Dawley rats maintained on either the control or lead acetate-containing diet for up to 79 weeks. Mean body weights at the end of the study were 723 g for the control rats and 585 g for the lead acetate-treated rats, although lifetime average weights were not presented. Because of the lack of these data across most studies (except Fowler and Lipsky, 1999), default body weight and feed and water consumption values were taken to be those presented by Gold and Zeiger (1997) in order to estimate the doses of lead to which the experimental animals were exposed. Gold and Zeiger derived values for body weights and feed consumption from the National Cancer Institute's 1976 bioassay of trichloroethylene (NCI, 1976) and for water consumption from the National Institute for Occupational Safety and Health (Sweet, DV (ed), 1993). Most of the bioassays of lead useful for quantitative risk assessment were conducted in rats. The default values for the male rat body weight, feed consumption, and water consumption are 0.5 kg (except Fowler and Lipsky, 1999; 0.4 kg), 0.02 kg_{feed}/day, and 0.025 kg_{water}/day, respectively, and for the female rat body weight and feed consumption are 0.35 kg and 0.0175 kg_{feed}/day, respectively. Body weight assumptions appear to be in line with those reported in the Kasprzak *et al.* study as well as that from information provided by breeders of experimental animals (Harlan, 2000). The default values for the male mouse body weight and feed consumption are 0.030 kg and 0.0036 kg_{feed}/day, respectively. Calculated dose rates for the lead bioassays are presented later in this document.

To estimate potency in animals (q_{animal}) from experiments of duration T_e, rather than the natural

lifespan of the animals (T), it is assumed that lifetime incidence of cancer increases with the third power of age:

$$q_{animal} = q_1^* \times (T/T_e)^3, \text{ for } T_e < T.$$

Following Gold and Zeiger (1997) and U.S. EPA (Anderson and U.S. EPA, 1983), the natural lifespan of mice and rats is assumed to be two years. For experiments of duration beyond this default assumption, no adjustment to the potency is made. So, for experiments lasting T_e weeks in these rodents, with $T_e < 104$ weeks,

$$q_{animal} = q_1^* \times (104/T_e)^3.$$

2.4.2 Interspecies Scaling

Once a potency value is estimated in animals following the techniques described above, human potency is estimated. As described in the California risk assessment guidelines (CDHS, 1985), a dose in units of milligram per unit surface area is assumed to produce the same degree of effect in different species in the absence of information indicating otherwise. Under this assumption, scaling to the estimated human potency (q_{human}) can be achieved by multiplying the animal potency (q_{animal}) by the ratio of human to animal body weights (bw_h/bw_a) raised to the one-third power when animal potency is expressed in units $(mg/kg\text{-}day)^{-1}$:

$$q_{human} = q_{animal} \times (bw_h / bw_a)^{1/3}.$$

As discussed above, body weights (bw_a) of 0.5 and 0.35 kg for male and female rats, respectively, and 0.03 kg for male mice were assumed (with the exception of the estimate of 0.4 kg for the Fowler and Lipsky study). Human body weight (bw_h) is assumed to be 70 kg.

2.4.3 Adjustment for Lead Content

Based upon the experimental findings from the administration of different lead compounds by different routes to experimental animals (IARC, 1980), it is reasonable to conclude that the lead component of these compounds is responsible for the renal carcinogenicity. Cancer potencies were calculated based upon dose rates adjusted for lead content using the molecular weight of the test compound to produce estimated risks based upon exposure to lead.

2.4.4 Adjustment for Chemical Form/Route

Since there are many substances that fall under the Proposition 65 listing of "lead and lead compounds," an effort was made to establish whether the carcinogenic potency of different lead compounds by the oral route could be established with confidence. Since reliable bioassay data by the relevant route is only available for two lead compounds, lead acetate and lead subacetate, it was reasonable to investigate which toxicokinetic parameters may influence the carcinogenicity. One possible influence is differences in gastrointestinal absorption of different lead compounds. The gastrointestinal absorption of lead has been reviewed recently (Diamond *et al.*, 1998). Among the influences on absorption identified in the review are the chemical form,

the contents of the gastrointestinal tract, diet and nutritional status, and age. Evidence in the literature, largely from short-term administration of lead compounds, suggests that different lead compounds do vary in absorption. In feeding studies lead is more readily absorbed by rats when administered as lead acetate than when administered as lead-containing mining waste (Freeman *et al.*, 1994). Other studies in F344 rats have shown that lead acetate and lead oxide in feed are more readily absorbed than lead sulfide or mining ore concentrate containing lead (Dieter *et al.*, 1993). In rats treated for two days with various lead compounds and examined for kidney lead content, absorption ranged approximately twelve-fold with metallic lead (particle size 180-250 µm) the least absorbed and lead carbonate which was the most absorbed (Barltrop and Meek, 1975). Lead octoate, lead naphthenate, lead sulfide, lead tallate, and lead acetate fell between these two in absorption. The physico-chemical property or properties which govern the gastrointestinal absorption of lead compounds are unclear based upon the available literature. Barltrop and Meek noted that "it is not possible to relate the observed differences in the other compounds to their solubility in biological fluids." Two lead compounds which differ considerably in water solubility, lead acetate and lead carbonate, are comparably absorbed (Humphreys, 1991). Thus, water solubility of the compounds does not appear to be a good predictor of absorption from ingestion of lead.

In light of the uncertainty regarding the relationship of chemical form to cancer potency, for purposes of cancer potency estimation, lead compounds will be considered equivalent based upon lead content. Since the estimation of risk in this assessment is based upon studies conducted with relatively highly absorbed lead compounds, the cancer potencies derived here may overestimate the potency of lead compounds which are less well absorbed.

Another concern is whether the kinetics of absorption of lead by oral exposure may influence the carcinogenic dose-response at the primary affected site, the kidney. Some experiments have suggested that gastrointestinal absorption of lead compounds is a saturable process in rats, particularly the study of Aungst *et al.* (1981). Rats orally exposed to 1 mg/kg_{bw} lead acetate absorbed 42% of the dose, whereas rats exposed to 100 mg/kg_{bw} lead acetate absorbed 2% of the dose. In the same study, rats administered lead in drinking water at concentrations ranging from 5-5000 mg/liter showed proportionally less absorption (as indicated by kidney and blood lead levels) with increasing dose, suggesting diminished capacity for absorption with increasing dose. In spite of these observations, the kidney tumors observed in male rats in the high-dose studies conducted by Azar *et al.* (1973) exhibited an increasing tumorigenic dose-response relationship within the range of doses examined by Aungst *et al.* (1981). The disposition of lead in both experimental animals and humans is complex, with significant accumulation of lead in bone, blood, and soft tissue compartments (ATSDR, 1993). Since the cancer endpoint is under consideration here, more information will be required before toxicokinetic data can be used confidently in departing from the linear assumption in the dose-response relationship. Dose considerations are made complicated by a number of factors. Considerable effort has gone into establishing the relationship between non-cancer toxicity and measures of lead exposure such as blood lead and lead body burden. Extending this relationship to the development of cancer is complicated by the findings of Waalkes *et al.* (1995). Their finding of renal tumors following perinatal exposures to lead (*in utero* and via dams' milk) suggests that carcinogenicity occurs in the absence of overt toxicity to the target organ as well as the likely absence of significant accumulation of lead compounds in the kidney and the rest of the body. This study also points to the possibility of increased sensitivity of the developing fetus and neonate to the carcinogenic

effects of lead.

Since lead does not undergo detoxifying metabolism in the body, but rather redistributes among several compartments in response to a number of factors prior to elimination, it is plausible that lead present in the body after exposure ceases, particularly that in the bone, will continue to present a risk when physiological conditions dictate its systemic release. Lead distribution appears to be equilibrium driven and the body/bone burden of lead would likely become an issue when both sufficient time and level of exposure has occurred to significantly raise bone lead levels and when exposure is reduced to such a level that equilibrium leads to release from bone stores during the course of bone formation and resorption. Since the kidney is the primary target of lead's carcinogenic action, knowing the level of redistribution to the kidney becomes important. A pharmacokinetic model in rats which incorporated bone modeling failed to adequately predict kidney lead levels following exposure in rats (O'Flaherty, 1991). The author concluded that "to model kidney lead, and especially biologically available kidney lead, will require a much fuller understanding of the age, sex, dose rate, and time dependence of specific lead binding in the kidney than we have now."

The animal studies from which cancer potencies were estimated here used continual exposure protocols, via either drinking water or feed. An increasing body burden of lead may not have contributed significantly to the renal tumor yield in these studies, since bone lead may not have been released due to continuously high systemic lead levels. Estimation of human risk using the potencies derived here (following interspecies scaling) will require a careful consideration of exposure and dose, taking into account both duration and intensity in order to weigh the possible contribution of stored lead to cancer risk. Presently, this evaluation would be difficult because of the complexity of lead toxicokinetics and the data gaps in this knowledge.

2.4.5 Calculation of Human Risk

To estimate human risk at low doses, human potency is multiplied by average daily dose. The risk estimate obtained is referred to by the U.S. EPA as "extra risk" (Anderson and U.S. EPA, 1983), and is equivalent to that obtained by using the Abbott (1925) correction for background incidence.

3. ESTIMATION OF CANCER POTENCY VALUES

For calculating cancer potencies, the dose rates in mg/kg-day were established based upon the lead compounds' concentrations in feed and water and the default assumptions or authors' estimates of body weights and feed and water consumption. Dose rates are presented in Table 4. Using the MSTAGE computer program (Crouch, 1992), animal potencies were estimated using the dose rates and tumor incidence data from those studies deemed suitable for quantitative analysis. The induction of kidney tumors was observed in several suitable studies in rats and a single study in mice. Only the control and low-dose findings from the mouse study were suitable for quantitative analysis because of the early high mortality in the high-dose group. The perinatal exposure studies of Waalkes *et al.* (1995), while showing a sensitivity of mice to the renal tumorigenic effects of lead, did not include lifetime exposure, and so were not included. Estimated animal potencies are shown in Table 4 and estimated human potencies are shown in Table 5.

Table 4. Dose rate calculations (in mg Pb/kg-day), study duration (in weeks), kidney tumor incidence and animal potency calculations (in (mg Pb/kg-day)$^{-1}$) based upon oral studies in rats and mice.

Study	Sex	Dose Rates (mg Pb/kg-day)	Duration (wks)	Tumor Incidence	q_1^* (mg/kg-day)$^{-1}$	q_{animal} (mg/kg-day)$^{-1}$
Rats						
Koller *et al*. (1985)	M	0, 130	76	0/10, 13/16	0.021	0.054
Azar *et al*. (1973)	M	0.12, 0.2, 0.72, 2.5, 5.6, 22, 45, 84	104	0/20, 0/100, 0/50, 0/50, 0/50, 5/50, 10/20, 16/20	0.0029	0.0029
	F	0.15, 0.25, 0.9, 3.1, 7.1, 27, 56, 105	104	0/20, 0/100, 0/50, 0/50, 0/50, 0/50, 0/20, 7/20	0.00044	0.00044
Fowler & Lipsky (1999)	M	0, 2.0, 10, 40	104	0/55, 0/42, 5/52, 24/41	0.015	0.015
Van Esch *et al*. (1962)	M	0, 15	126	0/14, 5/16	0.048	0.048
	F	0, 18	126	0/15, 6/16	0.048	0.048
	M	0, 146	104	0/13, 6/13	0.0079	0.0079
	F	0, 183	104	0/13, 7/11	0.01	0.01
Kasprzak *et al*. (1985)	M	0, 146	78	0/30, 13/29	0.0063	0.015
Mao and Molnar (1967)	M	0, 146	99	1/20, 31/40	0.014	0.016
Mice						
Van Esch & Kroes (1969)	M	0, 44	104	0/19, 6/20	0.0015	0.0015

Table 5. Cancer potencies of lead compounds. All potencies (q_{human}) are in units of (mg Pb/kg-day)$^{-1}$ and are based on oral studies in rats and mice showing the induction of kidney tumors.*

Compound	Study	Route	Sex	q_{human}
Lead acetate	Koller *et al.* (1985)	Drinking Water	Male	0.28
	Azar *et al.* (1973)	Feed	Male	0.015
			Female	0.0026
	Fowler & Lipsky (1999)	Drinking Water	Male	0.085
Lead subacetate	Van Esch *et al.* (1962)	Feed (low dose)	Male	0.25
			Female	0.28
		Feed (high dose)	Male	0.041
			Female	0.058
	Kasprzak *et al.* (1985)	Feed	Male	0.078
	Mao and Molnar (1967)	Feed	Male	0.084
	Van Esch & Kroes (1969) [mice]	Feed	Male	0.020

* Shaded boxes indicate potencies used to derive the no significant risk level. All but the Van Esch and Kroes (1969) study were performed in rats.

Selection of suitable cancer potency for human risk assessment generally follows from the identification of the most sensitive species, sex, and tumor site, bearing in mind the quality of the available studies. With regard to lead, the kidney is the major site of tumor induction in experimental animals. Since there are a number of available studies from which cancer potencies could be calculated, we chose to identify those with the highest quality experimental design. The Azar *et al.* (1973) and Fowler and Lipsky (1999) studies would appear to benefit from the administration of multiple doses to a relatively large number of animals, particularly in the lower dose levels in the case of Azar *et al.* (1973). In the Azar *et al.* study, renal tumors were observed only at doses of about 22 mg/kg-day and higher. However, in the Van Esch *et al.* (1962) studies, significant increases in renal tumors (>30% incidence) were observed at 15 and 18 mg/kg-day in male and female rats, respectively, leading to higher calculated potencies. Likewise, the Zawirska and Medras (1968, 1972) studies also show increased tumor incidences at an administered dose of lead acetate of 3 mg/day (= 6 mg Pb/kg-day for 0.5 kg rats).

Concerning other studies, the uncertainties regarding the experimental protocol as presented in the Mao and Molnar (1967) publication, particularly the ambiguity as to whether sacrifices were performed because of morbidity or because they were scheduled, reduces confidence in using the potency derived from this study. Thus, this study will not be considered further in establishing a human potency. There is less confidence in other studies due to poor experimental design (lack of reported controls in Nogueira (1987), Boyland *et al.* (1972), and Oyasu *et al.* (1970); use of seven month old animals at the start of the experiment in Zawirska and Medras (1972)), or limited reporting of data (the data from Zawirska and Medras (1968) is only available in summary from secondary sources, and Zawirska and Medras (1972) did not report the lifespan of the group of animals treated with lead acetate for life); thus potencies were not calculated.

Clearly the rat is a sensitive species and there has been limited testing in other species. The single study in mice from which a cancer potency was calculated produced a value which was within the range of that estimated from the studies in rats, suggesting that mice are not a more sensitive species than rats to the carcinogenic effects of lead. Therefore, studies in rats were used to develop a cancer potency estimate.

An appreciable sex difference in estimated potencies was not observed, with those from studies of male rats ranging from 0.015 to 0.28 $(mg/kg\text{-}day)^{-1}$ and those from female rats ranging from 0.0026 to 0.28 $(mg/kg\text{-}day)^{-1}$. The calculated potencies also do not indicate a difference based upon the two chemical forms studied, lead acetate and lead subacetate. Similarly, the two potencies derived from drinking water studies (0.085 and 0.28 $(mg/kg\text{-}day)^{-1}$) are not clearly different from those derived from feed studies (0.0026 to 0.28 $(mg/kg\text{-}day)^{-1}$). Thus, the available data provide neither a basis for confidently selecting a more sensitive sex of rat nor evidence of a more potent chemical form or route of exposure.

These carcinogenicity studies spanned lead doses in rats estimated from 0.12 to 183 mg/kg-day, a 1500-fold range. In deriving a potency for use in the NSRL calculation, studies conducted in the high dose range were considered less relevant, particularly in light of the non-linearity in the dose-response in this region. Thus, the following studies were excluded from further use in potency estimation: the high-dose studies of Van Esch *et al.* (1962), and the Kasprzak *et al.* (1985) and Koller *et al.* (1985) studies. Because of the uncertainty associated with the selection of the most suitable of the remaining studies, the potency was calculated based upon the geometric mean of the following group: the low dose studies of Van Esch *et al.* (1962) in male and female rats, the Azar *et al.* (1973) studies in male and female rats, and the Fowler and Lipsky (1999) studies in male rats [shaded potencies in Table 5]. This geometric mean potency (q_{human} as lead) is 0.047 $(mg/kg\text{-}day)^{-1}$.

4. CALCULATION OF RISK SPECIFIC INTAKE

4.1. Risk Specific Intake Level Calculation Method

The intake level (I, in mg/day) associated with a cancer risk R, from exposure to a carcinogen is

$$I = \frac{R \times bw_h}{q_{human}}$$

where bw_h is the body weight, and q_{human} the theoretical cancer potency estimate for humans.

Daily intake levels associated with lifetime cancer risks at or below 10^{-5} are considered to pose no significant risk of cancer under Proposition 65 (Title 22 California Code of Regulations, Section 12703). Thus for a 70 kg person, the intake level posing no significant cancer risk under Proposition 65 is given by

$$NSRL = \frac{10^{-5} \times 70\ kg}{q_{human}}$$

4.2. No Significant Risk Levels for Lead Compounds

Potency estimates, in units of $(mg/kg\text{-}day)^{-1}$, derived from data on tumor incidence after oral exposure of rats to lead compounds are shown in Table 5. The shaded boxes contain the estimates which form the basis for the recommended potency of 0.047 $(mg/kg\text{-}day)^{-1}$. Based on this potency, the intake level associated with lifetime cancer risk of 10^{-5} for lead is 15 µg/day. Based upon the molecular weights of specific lead compounds, this human cancer potency estimate for lead corresponds to oral route NSRLs of 23 µg/day for lead acetate, 41 µg/day for lead subacetate, and 58 µg/day for lead phosphate.

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