Carcinogenicity of Tetraethyl Lead

Tetraethyl lead (TEL) is an important, widely used, anti-knock additive for motor fuels. While the acute and subacute toxicity of TEL and other organic lead halides has been extensively studied[1,2], there is no available published information on carcinogenicity testing with these compounds. Results of preliminary experiments on the carcinogenicity of TEL are reported here.

Solutions of TEL, at concentrations of 1, 2 and 20 mg/ml in redistilled tricaprylin, were stored in sealed ampules at 4 °C and used within 1 week of preparation. By previously described techniques[3,4], solutions were injected s.c. in the nape of the neck of random-bred infant Swiss mice (ICR/Ha) at ages of 1, 7, 14 and 21 days in volumes of 0.1, 0.1, 0.2 and 0.2 ml respectively; controls received solvent alone (Table I). The uneven number of litters finally assigned to the various groups reflected an attempt to concentrate testing at the highest possible subtoxic drug concentration.

Following weaning and sexing, generally at 28 days, groups of 5 or fewer mice of each sex were housed in hanging metal cages with wire grid floors and given Purina chow and water ad libitum. Mice were inspected daily and weighed weekly for the first month of life and at monthly intervals thereafter. Mice were allowed to survive, with the exception of those sacrificed when sick or moribund, until experiments were terminated between 49 and 51 weeks.

Mortality before weaning (Table I) was comparable in solvent controls (15%) and in neonates receiving 0.1 mg of TEL on day 1 and a total dosage of 0.6 mg (20%). The 4 individual doses of TEL administered on days 1, 7, 14 and 21 in the latter group are equivalent to 50, 20, 20 and 13 mg/kg, if corresponding animal weights are taken as 2, 5, 10 and 15 g respectively. Higher mortality was, however, observed with 0.2 and 2.0 mg doses on day 1 (92% and 100% respectively). Death before weaning in all groups was generally restricted to the first week of life, so that mortality differences between the various groups also occurred then. Relative to controls, there was no evidence of weight loss in TEL-treated mice either at weaning or at the termination of experiments.

An enhanced incidence of lymphomas was noted in TEL-treated female mice (Table II). Five of 41 treated females (12%) surviving at 36 weeks developed lymphomas in contrast to none of 48 controls. Ignoring possible litter effects, $\chi^2 = 4.12$, $P < 0.05$. These 5 lymphomas were distributed in 3 of 10 TEL-treated litters. These tumors developed relatively late in life and were predominantly well differentiated lymphatic leukemias (Table II). There was no significant difference in the incidence of other tumors in TEL-treated and control mice.

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Table I. Toxicity induced in Swiss mice by neonatal s.c. injections of tetraethyl lead solutions in tricaprylin

Treatment group	Dosage (mg) on specified days following birth				Total dosage (mg)	No. of mice injected (corresponding No. of litters)	% mortality prior to weaning	Sex	No. of survivors at 49 weeks/No. of survivors at weaning
	1	7	14	21					
Solvent controls	–	–	–	–	–	124 (11)	15	M F	33/55 48/50
Tetraethyl lead	2.0	–	–	–	2.0	69 (6)	100	M F	– –
Tetraethyl lead	0.2	0.2	0.4	0.4	1.2	79 (7)	92	M F	3/5 1/1
Tetraethyl lead	0.1	0.1	0.2	0.2	0.6	109 (10)	20	M F	20/43 38/44

Table II. Malignant tumors induced in Swiss mice by neonatal injections of tetraethyl lead

Treatment group	Sex	No. of mice surviving at 36 weeks	% incidence of malignant tumors, based on survivors at 36 weeks		
			Lymphomas	Hepatomas	Fibrosarcomas
Solvent controls	M	39	3[a]	5	0
	F	48	0	0	0
Tetraethyl lead, 0.6 mg	M	26	4[b]	4	0
	F	41	12[c]	0	2

[a] 1 reticulum cell sarcoma at 51 weeks. [b] 1 lymphatic leukemia at 38 weeks. [c] 1 unclassifiable leukemia at 36 weeks; 3 lymphatic leukemias at 42, 48 and 51 weeks, respectively; 1 reticulum cell sarcoma at 51 weeks.

The absence of lead nephropathy or renal tumors in TEL-treated mice is of interest, in contrast to the induction of these effects in rats following prolonged administration of high levels of lead salts[5,6]. The relatively low toxicity of TEL, administered parenterally, to neonatal mice is noteworthy; the LD_{50} on day 1 of life is between 50 and 100 mg/kg, in contrast to an LD_{50} of between 16 and 24 mg/kg following oral administration in adult rats[1]. Possibly, the relative resistance of neonatal mice to TEL is due to immaturity in their microsomal liver enzymes with consequent failure to dealkylate TEL to its stable triethyl derivative, known to be more toxic[2]. At a total TEL dosage of 0.6 mg, one of limited toxicity, a weak carcinogenic effect is apparent. It should, however, be noted that the TEL-induced lymphomas occurred late in life, in contrast to the general tendency to earlier development of such tumors following administration of strong carcinogens to neonatal mice.

Zusammenfassung. Ein vermehrtes Vorkommen von Lymphomas zeigte sich bei mit Tetraäthylblei behandelten weiblichen Mäusen (12%) im Gegensatz zu den entsprechenden Kontrollen (0%). Die carcinogene Wirkung von Tetraäthylblei wurde durch parenterale Administration einer totalen Dosis von 0.6 mg an neugeborenen Schweizer Mäusen gezeigt.

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Anti-Inflammatory Action of a Benzyl Glucofuranoside Applied Topically

It has previously been demonstrated that 3,5,6-tri-*O*-benzyl-D-glucofuranoside[1] (henceforth referred to as benzyl glucofuranoside) displays anti-inflammatory actions following systemic (oral or parenteral) administration in a variety of experimental inflammatory reactions in the laboratory animal as well as in man[2–5]. In view of the pronounced lipophilic character of benzyl glucofuranoside, it seemed likely that the compound might easily be absorbed by the skin. The following account shows that benzyl glucofuranoside inhibits an inflammatory reaction of the skin when applied topically to the area in which this reaction is elicited. The procedure adopted was a slight modification of the method described by Tonelli et al.[6] by which the topical antiphlogistic effect of steroids can be assessed. With this method an acute inflammatory response is elicited by applying croton oil with an appropriate vehicle to the rat ear, and then quantitating it gravimetrically by comparison with the contralateral untreated ear. Co-application of an active compound results in a reduction of the weight increase.

The main modification consisted in the use of: (a) male mice of a body weight of 22–27 g instead of immature female rats, and (b) a reading time of 4 instead of 6 h following the application of the irritant.

The benzyl glucofuranoside was incorporated in graded concentrations in the vehicle containing the irritant. The effects of benzyl glucofuranoside were compared with those of a well-established antiphlogistic corticosteroid, hydrocortisone.

As may be seen from Table I, benzyl glucofuranoside is capable of reducing the increase in weight provoked in the mouse ear by topical application of croton oil. This anti-inflammatory effect of the compound shows a clear-cut dose-dependent behaviour, a concentration of 30 mg/ml producing a weight reduction which is already highly significant statistically. The ED_{50} determined graphically is 70 mg/ml.

In order to ascertain that the anti-inflammatory effect of benzyl glucofuranoside is not due to a non-specific

Table I.

Preparation	No.	Concentration (mg/ml)	Weight increase of the ear mg	± S.E.[a]	P[a]	Inhibitory effect (%)
Controls	15	–	27.2	1.6	–	–
Benzyl glucofuranoside	10	10	27.8	1.9	–	0
	10	30	19.3	1.5	< 0.001	29
	10	100	12.0	2.0	< 0.001	56
	10	300	3.8	0.8	< 0.001	86
Hydrocortisone	5	0.3	22.8	3.1	< 0.01	16
	10	1.0	14.1	1.5	< 0.001	48
	10	3.0	11.3	1.1	< 0.001	58
	10	10.0	5.7	0.9	< 0.001	79

[a] Mean ± S.E., and *P* calculated according to Lord.

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