LETTERS TO THE EDITOR

A STUDY OF CERTAIN SUBSTITUTED SULPHONOHYDRAZIDES FOR CARCINOGENICITY IN MICE*

Sir,—Roe et al. (Nature, Lond. 1967, 216, 375) examined hydrazine, methylhydrazine sulphate, 1,1-dimethylhydrazine, phenylhydrazine and p-hydrazinobenzoic acid for carcinogenic effects on mice. They found that hydrazine and 1,1-dimethylhydrazine increased the incidence of lung tumours, whereas the other hydrazines had no apparent carcinogenic effects. Searle (Chem. in Br. 1970, 6, 5) reported that diethylhydrazine and the antitubercular drug isonicotinic acid hydrazide produced tumours in some tests on mice (Juhasz et al. Z. Krebsforsch. 1957, 62, 188; Weinstein et al. J. Lab. clin. Med. 1962, 60, 1025; Biancifiori et al. Br. J. Cancer 1964, 18, 543). Since several arylsulphonohydrazides have fungicidal activity, for example against wheat rust, it appeared interesting to examine some of this class of compound for carcinogenicity. The present study concerns benzenesulphonohydrazide (BSH), 4-p-bromophenoxybenzenesulphonohydrazide (BPBSH) (Cremlyn, J. chem. Soc. (C), 1967, p.77), N4-acetylsulphanily1 hydrazide (ASH) (Cremlyn, J. chem. Soc. 1962, p.2133) and 4-chloro-3-(N-sulphonylhydrazino)benzoic acid (CSHBA) (Cremlyn, J. chem. Soc. (C) 1968, p.11).

Female Swiss mice, 8 wk old, were divided into five groups each consisting of 30 mice. Group I was given 2 mg BSH in 0.2 ml 3% aqueous gelatin by gastric instillation for 5 doses/wk for 4 wk, followed by 3 doses/wk to a total of 158 doses. Group II was similarly given BPBSH for 5 doses/wk for 4 wk, followed by 3 doses/wk to a total of 54 doses. Group III received 22 doses of ASH similarly; then because of toxicity, treatment was suspended for 12 wk, and then started again using 1 mg in 0.2 ml 3% aqueous gelatin for 3 doses/wk for a further 102 doses. Group IV received 5 doses of CSHBA weekly for 4 wk, then 3 doses/wk to a total of 52 doses. Group V—the control mice—were given 0.2 ml 3% aqueous gelatin at a rate of 5 doses/wk for 4 wk, followed by 3 doses/wk to a total of 158 doses. The survivors in the five groups were killed after 60 wk and examined post mortem, and the results are summarized in Table 1.

Application of the chi-squared method of statistical evaluation to these results indicated that the difference between the total of 13 out of 95 mice in Groups I–IV and the 1 out of 29 controls with lung tumours is not significant (0.1 < P < 0.2); neither is the difference between 6 out of 95 treated mice and 1 out of 29 controls with liver tumours (P > 0.2). Larger scale

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Table 1. Tumour incidence in female mice 60 wk after the start of treatment with substituted sulphonohydrazides

<table>
<thead>
<tr>
<th>Test compound</th>
<th>No. of survivors at wk 60*</th>
<th>No. of survivors with Pulmonary tumours</th>
<th>Liver-cell tumours</th>
<th>Other neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>29</td>
<td>1</td>
<td>1</td>
<td>2†</td>
</tr>
<tr>
<td>BSH</td>
<td>24</td>
<td>4</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>BPBSH</td>
<td>27</td>
<td>1</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>ASH</td>
<td>21</td>
<td>1</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>CSHBA</td>
<td>23</td>
<td>7</td>
<td>1</td>
<td>—</td>
</tr>
</tbody>
</table>

* Each group originally consisted of 30 animals.
† One subcutaneous sarcoma and one malignant lymphoma.

tests might show that compounds BSH and CSHBA have marginal tumorigenic activity, but on the evidence presented here it can be concluded that none of the four aryl sulphonohydrazides is a potent carcinogen for mice. It was found that an inflammatory lung disease present in a large proportion of the control mice was apparently absent from all the treated animals, suggesting that the compounds have anti-microbial activity.

R. J. W. CREMLYN,
Department of Chemical Sciences,
Hatfield Polytechnic,
Hatfield,
Hertfordshire, England

F. J. C. ROE,
Chester Beatty Research Institute,
Institute of Cancer Research,
Royal Cancer Hospital,
Fulham Road,
London, S.W.3, England

THE METABOLISM OF BHT BY MAN

Sir,—The comments appended to the review elsewhere in this issue (p. 296) of the letter by Holder et al. (J. Pharm. Pharmac. 1970, 22, 375) have stimulated us to examine the differences that exist between ourselves and these authors on the metabolism of BHT by man.

We are inclined to agree with your reviewer that the different results obtained in the two laboratories should not lead to the conclusion that different metabolic pathways are involved in the metabolism of BHT by man in England and in Australia. Only four human subjects were involved in the Australian investigation, and in our work (Daniel et al. Biochem. J. 1968, 106, 783) only two men were studied in detail. It is, therefore, possible, though unlikely, that there is a wide variation in the way BHT is metabolized by man, but that the number of men involved in these studies was not large enough to reveal this.