Hepatic 7-Alkoxycoumarin O-Dealkylase in Mice: Induction by \(\beta\)-Naphthoflavone of Hepatic Enzyme Activity

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Abstract—Hepatic 7-alkoxycoumarin O-dealkylation activities in control and \(\beta\)-naphthoflavone-pretreated mice were determined. The O-demethylation and O-deethylation activities of 7-alkoxycoumarin in control mice were almost the same values, while the O-depropylation activity was lower than those of the other reactions. The O-dealkylase activity varied markedly among the 18 strains of mice surveyed, and strain-dependent differences in the cytochrome P-450 content were also detected among the strains. \(\beta\)-Naphthoflavone induced O-dealkylation activity, especially O-deethylation and O-depropylation activities, only in ddY, DS and its substrains (A2–3, A3–1, C1–2 and Nh/+), C3H/He and C57BL/6J strains, but not in DBA/2, BALB/c and KYF/2 strains. The former strains of mice are thus classified as “responsive strains” to \(\beta\)-naphthoflavone and the latter as “non-responsive strains”. The O-dealkylase activity in other strains of mice were not clear in responsiveness to \(\beta\)-naphthoflavone. The hepatic cytochrome P-450 content in responsive strains also increased upon pretreatment of the animals with \(\beta\)-naphthoflavone. The results indicate marked strain differences in basal and \(\beta\)-naphthoflavone-induced activity of hepatic 7-alkoxycoumarin O-dealkylase in mice.

The O-dealkylation reaction of 7-alkoxycoumarin is known to be catalyzed by cytochrome P-450 (1, 2). Recent studies have indicated a marked alteration in the substrate specificity and the specific activity of the microsomal O-dealkylation reaction when rats are pretreated with specific inducers (3–6). Administration of 3-methylcholanthrene or \(\beta\)-naphthoflavone markedly increases the O-dealkylation activity of 7-ethoxy- and 7-propoxy-coumarins, but not of 7-methoxycoumarin, in both isolated microsomes and whole liver homogenate (3, 5, 6).

The existence of multiple forms of cytochrome P-450 in liver microsomes has been established by many investigators (7, 8). Administration of various chemicals causes selective induction of one or more forms of the cytochrome, depending on the chemicals. When rats are employed as experimental animals, 3-methylcholanthrene or \(\beta\)-naphthoflavone induces cytochrome P-448 (designated as P-448, P-450, MC-B, DE-II and so on by several investigators), which is preferentially active towards benzo(a)pyrene (8–12). Increase of O-dealkylation activity of 7-ethoxy- and 7-propoxy-coumarins by the administration of polycyclic hydrocarbons (3, 5, 6) probably indicates that the reaction is catalyzed by cytochrome P-448, similar to benzo(a)pyrene metabolism. Nebert and co-workers have indicated the existence of strain differences in the inducibility of hepatic benzo(a)pyrene hydroxylase in mice by 3-methylcholanthrene (13–15). It is thus interesting to determine the strain differences in the inducibility of 7-alkoxycoumarin O-dealkylase in mouse liver for comparison with that of benzo(a)pyrene hydroxylase.

In the present study, the inducibility of hepatic 7-alkoxycoumarin O-dealkylase was determined in 18 strains of mice. As described by Nebert et al. (13–15), \(\beta\)-naphthoflavone induced hepatic O-dealkylase activity only in some responsive strains to varying degrees. Increases in the O-deethylation and O-
depropylation activities, but not in the O-demethylation activity, of 7-alkoxycoumarin were observed in the responsive strains of mice with administration of \( \beta \)-naphthoflavone as in the inductive pattern in rats.

### Materials and Methods

#### Animals and their treatments: Male adult

![Diagram of mouse strains]

**Fig. 1.** List of mice strains used. The 18 strains of mice used are classified arbitrarily into 3 groups. Group I: The animals in this group are derived from German mouse, dd strain. The animals of the DS strain and its sublines (A2–3, A3–1 and C1–2) were bred at the farm of Shionogi Research Laboratories (more than 90 generations). Non-hair mutant of DS, Nh/+(DS-Nh), was also bred at the farm (more than 20 generations). Group II: Animals classified in this group were established in the U.S.A. Relationships among these strains have been described previously (16). Group III: Animals not classified in the above two groups. KYB, KYC and KYF/2 strains were recombinant inbred ones of dd, NC, A/J and CBA strains.
animals (9–11 weeks old) of inbred strains were used for the experiments, unless otherwise stated. The following 18 strains were selected: ddY, DS, A2-3, A3-1, C1-2, NHf+/-, DBA/2, CBA, C3H/He, C3HeB/Fe, BALB/c, A/J, C57BL/6J, Slc-ICR, Jcl-ICR, KYB, KYC and KYF/210 (Fig. 1). Three of them (ddY, Slc-ICR and Jcl-ICR) were closed colony strains, and the animals from these strains were used without selection. Only for the A2-3 strain were female animals employed. Mice of ddY and Slc-ICR strains were obtained from Shizuoka Laboratory Center (Hamamatsu), Jcl-ICR, from Japan Clea Co. (Shiga), and KYF/2, from Funahashi Nojo (Chiba). Other strains were bred at the farm of Shionogi Research Laboratories. The animals were kept in an air-conditioned room (25±1°C, 50–60% humidity) which was lighted 12 hr a day (8:00–20:00) and maintained on commercial rat chow (Ca-1, Japan Clea Co., Tokyo) and water ad libitum. All animals were allowed at least 7 days to become acclimatized to the housing conditions prior to use in the experiments.

Some of the animals were given intraperitoneal administration of 9-naphthoflavone in sesame oil (80 mg/kg body weight), twice every two days, and used for the experiments 2 days after the last administration. In some cases, mice received single intraperitoneal injections of various amounts of 9-naphthoflavone and were killed one day later. Control animals received the same volume of sesame oil alone.

Preparation of enzyme samples: Non-fasted animals were killed by decapitation. Livers were removed quickly, weighed and homogenized in 0.25 M sucrose containing 50 mM Tris-HCl buffer (pH 7.4), 100 mg wet weight equivalent of tissue/ml, and then it was filtered through two layers of coarse gauze to remove the undispersed connective tissue. The resulting filtrate was used for the enzyme assay at the homogenate level. When liver microsomes were required for the assay, they were prepared from pooled livers of three-four mice using a preparation medium containing 0.154 M KCl and 150 mM Tris-HCl buffer, pH 7.4 (5). The protein concentration of isolated microsomes was determined by the method of Lowry et al. (17) using bovine serum albumin as a standard.

Determination of O-dealkylase activity and cytochrome content: 7-Alkoxycoumarin O-dealkylase activity in liver homogenate and isolated microsomes was determined by the PCA-precipitation method. Cytochrome P-450 content in liver homogenate was detected as described previously (18), and its concentration was calculated using the molar extinction difference of 104 mM−1 cm−1 for the absorption difference between the peak position (at about 450 nm) and 490 nm (19). Cytochrome P-450 content in isolated microsomes was determined according to the method of Omura and Sato (20). Micromosomal cytochrome b5 was determined as reported previously (21).

Chemicals: 7-Hydroxycoumarin O-methyl, O-ethyl and O-propyl derivatives were synthesized as described previously (5). NADP, glucose 6-phosphate and glucose 6-phosphate dehydrogenase were purchased from Oriental Yeast Co. (Tokyo). Other chemicals of the purest grade available were obtained commercially and used for the experiments without further purification.

Results

Hepatic 7-alkoxycoumarin O-dealkylase in various strains of mice: Cytochrome P-450-dependent monooxygenase activity in mouse liver was determined using the O-dealkylation reaction of 7-alkoxycoumarin as a model substrate. When mouse liver homogenate was employed as an enzyme source for the assay, almost the same activity was detected for both O-demethylation and O-deethylation reactions, while the O-depropylation activity was generally lower than those of the other reactions (Table 1). Interestingly, a remarkable difference in the specific activity of the O-dealkylation reaction was detected in the 18 strains of mice surveyed. Cytochrome P-450 content in mouse liver also differed markedly in the various strains of animals. However, no correlation was found between the cytochrome P-450 content and the specific
activity of the O-dealkylation reaction: the O-dealkylation activity in the DS strain differed markedly from that of ddY, although the cytochrome P-450 content was almost the same (Table 1). The results suggested that the composition of various forms of cytochrome P-450 differed among the various strains of mice.

Induction of hepatic 7-alkoxycoumarin O-dealkylase by β-naphthoflavone: Nebert and co-workers have indicated a marked strain difference of mice in the inducibility of hepatic benzo(a)pyrene hydroxylase by 3-methylcholanthrene (13-15). Thus, we studied the effect of β-naphthoflavone administration on hepatic 7-alkoxycoumarin O-dealkylase in mice to compare the characteristics of various strains of mice with the aforementioned results. Administration of β-naphthoflavone to mice in Group I (6 strains) led to a marked increase in the O-deethylation and O-depropylation activities, especially in the O-depropylation activity, while the O-demethylation activity showed only slight alteration (Fig. 2A). As shown in the figure, cytochrome P-450 content also increased with administration of β-naphthoflavone, although the extent of the increase was small compared with those in the O-deethylation and O-depropylation activities.

When β-naphthoflavone was administered to the mice in Group II, marked increases in the O-deethylation and O-depropylation activities and cytochrome P-450 content, as detected in the mice of Group I, were observed only in the C57BL/6J strain. Interestingly, slight alteration in the O-dealkylase activity and cytochrome content by β-naphthoflavone was observed in the DBA/2 strain, but no specific increases were found in the O-deethylation and O-depropylation activities. The O-dealkylase activity and cytochrome P-450 content in other strains of mice in Group II were not affected or slightly stimulated by

### Table 1. Hepatic 7-alkoxycoumarin O-dealkylase activity in various strains of mice

| Mouse strain | No. of mice | 7-Methoxycoumarin O-demethylease (nmol/min/g liver) | 7-Ethoxycoumarin O-deethylase (nmol/min/g liver) | 7-Propoxycoumarin O-depropylase (nmol/min/g liver) | Cytochrome P-450 (nmol/g liver) |
|--------------|-------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|--------------------------------|
| (1) Group I  |             |                                                 |                                                 |                                                 |                                |
| ddY          | 9           | 106.7±4.3 (1.00)                                | 104.1±4.5 (0.95)                                | 28.3±2.6 (0.27)                                 | 52.4±1.5                      |
| DS           | 5           | 53.5±2.3 (1.00)                                 | 49.9±2.4 (0.93)                                 | 18.4±0.8 (0.34)                                 | 50.1±1.6                      |
| A2-3         | 5           | 98.2±2.6 (1.00)                                 | 103.2±2.3 (1.05)                                | 42.9±1.6 (0.44)                                 | 46.0±2.4                      |
| A3-1         | 5           | 62.0±4.1 (1.00)                                 | 64.6±5.1 (1.04)                                 | 21.8±3.1 (0.35)                                 | 43.8±3.2                      |
| C1-2         | 4           | 74.8±2.1 (1.00)                                 | 93.0±6.7 (1.24)                                 | 48.9±5.2 (0.65)                                 | 64.1±4.2                      |
| NH/+         | 5           | 72.6±1.0 (1.00)                                 | 68.1±1.3 (0.94)                                 | 25.5±0.6 (0.35)                                 | 36.1±2.2                      |
| (2) Group II |             |                                                 |                                                 |                                                 |                                |
| DBA/2        | 6           | 112.1±4.7 (1.00)                                | 110.9±6.5 (0.99)                                | 51.6±3.7 (0.46)                                 | 44.1±1.7                      |
| CBA          | 3           | 89.1±2.8 (1.00)                                 | 100.7±2.9 (1.13)                                | 74.5±15.4 (0.84)                                | 51.6±1.5                      |
| C3H/He       | 5           | 71.2±1.4 (1.00)                                 | 71.4±1.9 (1.00)                                 | 30.1±1.0 (0.42)                                 | 36.3±1.1                      |
| C3HeB/Fe     | 3           | 99.7±4.1 (1.00)                                 | 106.8±4.4 (1.07)                                | 62.2±14.0 (0.62)                                | 51.9±1.5                      |
| BALB/c       | 4           | 103.8±2.3 (1.00)                                | 107.2±3.7 (1.03)                                | 41.4±3.1 (0.40)                                 | 41.7±4.7                      |
| A/J          | 4           | 108.4±7.6 (1.00)                                | 135.1±21.3 (1.25)                               | 68.4±16.7 (0.63)                                | 39.2±1.1                      |
| C57BL/6J     | 5           | 63.4±2.5 (1.00)                                 | 73.7±1.8 (1.16)                                 | 35.0±2.2 (0.55)                                 | 32.0±1.5                      |
| (3) Group III|             |                                                 |                                                 |                                                 |                                |
| SIC-ICR      | 5           | 87.2±3.4 (1.00)                                 | 84.8±5.4 (0.97)                                 | 86.5±3.4 (0.99)                                 | 59.4±5.9                      |
| Jcl-ICR      | 5           | 69.4±1.7 (1.00)                                 | 69.2±5.2 (1.00)                                 | 25.6±4.8 (0.37)                                 | 39.4±2.7                      |
| KYB          | 4           | 89.4±1.6 (1.00)                                 | 90.7±2.5 (1.01)                                 | 37.2±1.1 (0.42)                                 | 38.6±1.8                      |
| KYC          | 3           | 102.5±7.0 (1.00)                                | 108.0±8.1 (1.05)                                | 41.1±2.3 (0.40)                                 | 49.3±0.3                      |
| KYF/2        | 10          | 91.2±3.1 (1.00)                                 | 112.1±4.6 (1.23)                                | 48.5±2.1 (0.53)                                 | 47.7±1.1                      |

The values in the Table represent the mean±S.E., and the number in parentheses is the ratio of the O-dealkylase activity to that of the corresponding O-demethylease.
β-naphthoflavone administration under the experimental conditions employed (Fig. 2B). Hepatic cytochrome P-450-dependent 7-alkoxycoumarin O-dealkylase in most strains of mice in Group III was not stimulated clearly by β-naphthoflavone treatment. Slight increase in the activity was detected only in KYB and KYC strains in Group III (Fig. 2C).

As shown in Fig. 2, β-naphthoflavone-induced activity of hepatic 7-alkoxycoumarin
O-dealkylase is strain-dependent in mice. Of the 18 strains of mice employed, seven strains (ddY, DS, A2-3, A3-1, C1-2, Nh/+ and C57BL/6J) were classified clearly as being "responsive" to β-naphthoflavone treatment, and the O-dealkylase activity in these strains were stimulated by pretreating the mice with β-naphthoflavone. On the other hand, the activity in three strains of mice (DBA/2, A/J and KYF/2) was not affected by β-naphthoflavone administration, and thus, these strains of mice were classified as "non-responsive". Under the experimental conditions employed, some other strains of mice seemed to be responsive, but to a lesser extent in the increase of the O-dealkylase activity. In the case of closed-colony animals (ICR strain), where the population is heterogeneous, some mice were responsive but others were non-responsive. Administration of β-naphthoflavone also increased liver weight, with a significant increase being observed only in responsive mice strains (data not shown).

Alteration of microsomal 7-alkoxycoumarin O-dealkylase activity following administration of β-naphthoflavone: Liver microsomal 7-alkoxycoumarin O-dealkylase activity in control and β-naphthoflavone-pretreated mice was determined to obtain further information on the strain differences in the induction of hepatic O-dealkylase by β-naphthoflavone. Mice strains employed for this study were selected based on the results shown in Fig. 2. The O-dealkylation activity and cytochrome content in liver microsomes prepared from control mice clearly showed strain differences as observed in the homogenate system. Pretreatment of mice with β-naphthoflavone markedly increased microsomal O-deethylation and O-depropylation activities, but not O-demethylase activity, in DS and C57BL/6J strains. Microsomal cytochrome P-450 content in these strains showed higher values. Similar effects of β-naphthoflavone were observed in liver microsomes obtained from the C3H/He strain (Table 2). On the other hand, microsomal O-dealkylase activity in DBA/2, BALB/c and Slc-ICR strains was not affected much by β-naphthoflavone pretreatment. Cytochrome P-450 content in these strains was also not altered by this treatment (Table 2).

Pretreatment of mice with various amounts of β-naphthoflavone: To compare the responsibility of hepatic 7-alkoxycoumarin O-dealkylase to β-naphthoflavone, the animals were given single intraperitoneal injection of various amounts of β-naphthoflavone, and the hepatic O-dealkylase activities were determined. As shown in Fig. 3, the activities of both O-deethylation and O-depropylation reactions in three strains (DS, C57BL/6J and C3H/He) increased gradually with increasing doses of β-naphthoflavone. The most remarkable increase in the O-dealkylase activities were observed in the DS strain among the five strains surveyed. Increase of the activity by β-naphthoflavone administration was observed predominantly in the O-depropylation reaction compared with that of O-deethylation (Fig. 3). Hepatic cytochrome P-450 (P-448) also showed dose-dependent increase in these strains, but the O-demethylation activity increased only slightly (data not shown). On the other hand, hepatic O-dealkylase activity and cytochrome P-450 content in non-responsive strains (DBA/2 and BALB/c) were unaffected or even slightly stimulated by the administration of a high amount (150 mg/kg) of the inducer (Fig. 3). Increases of both O-deethylation and O-depropylation activities in DS, C57BL/6J and C3H/He strains were statistically significant (data of statistical analyses are not shown in the figure).

Discussion

Species and strain differences in drug metabolism have been established by many investigators. The existence of species differences in the 7-alkoxycoumarin O-dealkylation reaction was also demonstrated previously (5, 22). Thus, it was interesting to determine the O-dealkylase activity in various strains of mice to clarify the strain differences in the O-dealkylase system. As shown in Tables 1 and 2, the O-dealkylase activities and cytochrome P-450 content in both liver homogenate and isolated microsomes prepared from control animals varied markedly among the strains, indicating the existence of strain differences in hepatic 7-alkoxycoumarin O-dealkylase. Administration of a
Table 2. Effect of β-naphthoflavone administration upon liver microsomal O-dealkylase activity in various strains of mouse

| Mouse strain | Pretreatment of mouse | 7-Alkoxycoumarin O-dealkylase (nmol/min/mg protein) | Cytochrome content (nmol/mg protein) |
|--------------|-----------------------|---------------------------------------------------|-------------------------------------|
|              |                       | 7-Methoxycoumarin O-demethylase | 7-Ethoxycoumarin O-deethylase | 7-Propoxyoxycoumarin O-depropylase | Cytochrome P<sub>450</sub> | Cytochrome b<sub>5</sub> |
| DS           | Control               | 2.12±0.28                                      | 1.64±0.18                          | 0.54±0.04                          | 1.20±0.08                          | 0.43±0.04                          |
|              | β-NF                  | 1.97±0.16 (0.93)                               | 3.01±0.22** (1.84)                | 1.54±0.12** (2.85)                | 1.61±0.09* (1.34)                  | 0.54±0.04 (1.26)                   |
| C57BL/6J     | Control               | 1.93±0.09                                      | 2.36±0.08                          | 1.03±0.03                          | 1.00±0.03                          | 0.44±0.01                          |
|              | β-NF                  | 2.69±0.31 (1.39)                               | 4.93±0.55** (2.09)                | 2.80±0.21** (2.72)                | 1.59±0.14* (1.59)                  | 0.70±0.06* (1.59)                  |
| C3H/He       | Control               | 2.66±0.19                                      | 1.71±0.11                          | 0.59±0.04                          | 1.33±0.10                          | 0.42±0.01                          |
|              | β-NF                  | 2.84±0.08 (1.07)                               | 2.88±0.07** (1.68)                | 1.31±0.05** (2.22)                | 1.32±0.04* (1.37)                  | 0.61±0.01** (1.45)                 |
| BALB/c       | Control               | 1.95±0.10                                      | 2.17±0.17                          | 0.82±0.05                          | 1.01±0.04                          | 0.38±0.02                          |
|              | β-NF                  | 2.07±0.08 (1.06)                               | 2.70±0.14 (1.24)                  | 1.04±0.08 (1.27)                  | 1.15±0.06 (1.14)                   | 0.46±0.02* (1.21)                  |
| DBA/2        | Control               | 3.42±0.54                                      | 3.09±0.49                          | 1.49±0.29                          | 1.29±0.09                          | 0.45±0.03                          |
|              | β-NF                  | 3.54±0.47 (1.04)                               | 3.37±0.39 (1.09)                  | 1.55±0.18 (1.04)                  | 1.33±0.13 (1.03)                   | 0.49±0.03 (1.09)                   |
| S1c-ICR      | Control               | 3.32±0.15                                      | 2.55±0.13                          | 0.81±0.04                          | 1.71±0.07                          | 0.56±0.03                          |
|              | β-NF                  | 3.54±0.11 (1.07)                               | 3.20±0.15* (1.25)                 | 1.06±0.09 (1.31)                  | 1.83±0.06 (1.07)                   | 0.63±0.01 (1.13)                   |

The animals in control and β-naphthoflavone (β-NF) pretreatment groups received sesame oil and β-naphthoflavone, respectively, as described in "Methods". The values in the Table represent the mean±S.E. of 3 different preparations of microsomes. The number in parentheses is the ratio of the activity or the content to the corresponding O-dealkylase activity or cytochrome content in the control group. *Statistically significant (P<0.05) against the control group. **Statistically significant (P<0.01) against the control group.
typical inducer, phenobarbital, to various strains of mice resulted in increases in the \( \frac{0}{2} \)-dealkylase activities and cytochrome P-450 content in all strains of mice surveyed (data not shown). However, the increasing rate in the \( \frac{0}{2} \)-dealkylase activity clearly varied among the different strains. Similar results were obtained by Wood and Taylor (23, 24) who demonstrated that phenobarbital-induced activity of hepatic coumarin hydroxylase is strain-dependent.

Remarkable strain differences were observed in the induction of hepatic \( \frac{7}{2} \)-alkoxycoumarin \( \frac{0}{2} \)-dealkylase by \( \beta \)-naphthoflavone: hepatic \( \frac{0}{2} \)-dealkylase was markedly induced only in ddY, DS, A2-3, A3-1, C1-2, Nh/+, C3H/He and C57BL/6J strains among the 18 strains surveyed (Figs. 2 and 3). Since the animals of ddY, DS, A2-3, A3-1, C1-2 and Nh/+ strains are derived from German mouse, dd strain (Fig. 1), these animals are supposed to have a common character (gene) to respond to \( \beta \)-naphthoflavone. On the other hand, the \( \frac{0}{2} \)-dealkylase activity in DBA/2 and some strains were not affected by \( \beta \)-naphthoflavone pretreatment (Figs. 2 and 3), and the animals in these strains are not correlated genetically to the responsive strains (Fig. 1). The results suggest genetic regulation of the responsibility of hepatic \( \frac{7}{2} \)-alkoxycoumarin \( \frac{0}{2} \)-dealkylase to \( \beta \)-naphthoflavone. Genetic regulation of the responsibility of the hepatic benzo(a)pyrene hydroxylase system to 3-methylcholanthrene or other polycyclic hydrocarbons has been studied in detail using various strains of mice (13-15, 25, 26). The results showing the responsibility of hepatic \( \frac{7}{2} \)-alkoxycoumarin \( \frac{0}{2} \)-dealkylase to \( \beta \)-naphthoflavone in various strains of mice (Figs. 2 and 3, and Table 1) agreed with the aforementioned reports, suggesting that the \( \text{Ah} \) locus controls the induction of hepatic \( \frac{7}{2} \)-alkoxycoumarin \( \frac{0}{2} \)-dealkylase. Recent studies by Nebert have shown that the induction of several monooxygenase activities, including benzo(a)pyrene hydroxylase and \( \frac{7}{2} \)-ethoxycoumarin \( \frac{0}{2} \)-deethylase, is closely associated with the \( \text{Ah}^b \) allele (15). The results suggested that the activities of both benzo(a)pyrene hydroxylation and \( \frac{7}{2} \)-alkoxycoumarin \( \frac{0}{2} \)-dealkylation increase by the administration of polycyclic hydrocarbons only in the responsive strains of mice, and the present results agree with this.

When hepatic \( \frac{7}{2} \)-alkoxycoumarin \( \frac{0}{2} \)-
dealkylase activity was determined using rat samples, marked increases in the 0-deethylation and 0-depropylation activities were observed by pretreatment of animals with 3-methylcholanthrene or β-naphthoflavone (5, 6, 22). Similar results were obtained in responsive strains of mice (Figs. 2 and 3). The results suggest that β-naphthoflavone-inducible form(s) of cytochrome P-450 in responsive strains of mice has almost the same catalytic properties as that in rats. We do not presently know the properties of the cytochrome P-450's which catalyze the 0-dealkylation reaction of 7-alkoxycoumarin in mouse livers. Resolution and purification of the cytochrome P-450 monooxygenase system from responsive and non-responsive strains should provide valuable information on the regulation of 7-alkoxycoumarin O-dealkylation and the oxidative metabolism of other drugs.

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