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A mathematical approach to benzo[a]pyrene-induced hematotoxicity

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Abstract. Benzo[a]pyrene (BaP) has been reported to exert a differential effect on murine hematopoiesis that is mouse strain specific. Interpretation of these results based solely on experimental data is restricted and leaves important questions unanswered. Therefore, a mathematical model of murine hematopoiesis was applied in order to: (1) identify the targets of BaP, (2) quantify the damage to target cells and (3) based on these results, interpret differences in strain susceptibility. Model analysis of the hematopoietic response of D2 and BDF_1 mice to a daily oral administration of 125 mg/kg BaP showed that proliferating hematopoietic cells are the targets of BaP. Within this group it was found that: (a) erythropoietic cells were the most susceptible to BaP, (b) granulopoietic cells showed a susceptibility half that of erythropoietic cells and (c) the susceptibility of stem cells ranged between that of erythropoietic and granulopoietic cells. This damage pattern was the same for both strains, indicating that the difference between the strains was quantitative. As cell destruction rates were about 3-fold higher for D2 than BDF_1 mice, it was concluded that D2 mice were about three times as susceptible to BaP as BDF_1 mice. The study showed that the mathematical model, in addition to experimental methods, provided an efficient tool for the analysis of BaP hematotoxicity.

Key words: Benzo[a]pyrene – Mathematical model – Hematopoiesis

Introduction

Benzo[a]pyrene (BaP) is a ubiquitous polycyclic aromatic hydrocarbon (PAH) that exhibits a wide range of adverse toxicologic effects in animals as well as humans. Numerous studies have described its carcinogenic, mutagenic and teratogenic potency (reviewed in IARC 1983; Nebert 1989; Collins et al. 1991).

In general, BaP-mediated toxicity is paralleled by Ah responsiveness, with bone marrow toxicity being an important exception: Ah-responsive mice have a greater susceptibility to benzo[a]pyrene-initiated subcutaneous sarcomas than non-responsive mice but they are extremely resistant to oral benzo[a]pyrene-induced hematotoxicity (Nebert et al. 1977; Nebert and Jensen 1979). Anselstetter and Heimpel (1986) performed a detailed study on the evolution of BaP-induced hematopoietic changes in C57Bl/6 × DBA/2 (BDF_1) and DBA/2 (D2) mice. They found that a daily oral dose of 120 mg/kg BaP led to marked changes in hematopoiesis in D2 mice, i.e. severe decreases of pluripotent stem cells as well as erythropoietic and granulopoietic precursor cells. BDF_1 mice also showed marked changes in stem cells and erythropoietic precursors; however, the overall decreases were less pronounced and there were no significant changes in granulopoietic precursors.

Even though the basis for the strain-dependent difference in BaP-induced hematotoxicity was identified by Nebert and co-workers to be the result of genetically determined effectiveness of first pass elimination (Nebert et al. 1977, 1980; Legraverend et al. 1983), the available hematological data still leave important questions open. First, is it possible to identify the hematopoietic targets of BaP? Is it correct to conclude that whereas stem cells, erythropoietic and granulopoietic cells were destroyed in D2 mice, in BDF_1 mice granulopoietic cells were not destroyed by BaP? Second, to what extent do changes in cell number reflect treatment-dependent cytotoxicity and to what extent do they reflect treatment-induced compensatory mechanisms? And finally, is it possible to quantify cell distruction rates in different cell stages?

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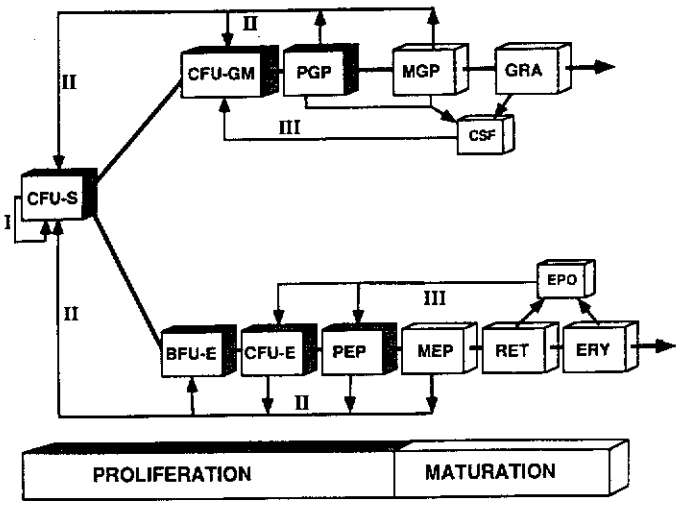

Fig. 1. Structure of the model: granulopoiesis and erythropoiesis are descendent from stem cells (CFU-S). Thrombopoiesis is not considered. Hematopoiesis is regulated by three types of feedbacks. Feedback I: autoregulation of stem cells. Feedback II: intramedullary feedback from erythropoietic and granulopoietic bone marrow cells to CFU-S, BFU-E, and CFU-GM. Feedback III: feedback from reticulocytes (*RET*) and erythrocytes (*ERY*) to CFU-E and proliferating erythropoietic precursor cells (*PEP*); feedback from proliferating (*PGP*) and maturing (*MGP*) granulopoietic precursors and granulocytes (*GRA*) to CFU-GM. The hormones involved in erythropoiesis and granulopoiesis are denoted by *EPO* (eryhtropoietin) and *CSF* [colony stimulating factor(s)] respectively

These questions cannot be answered by experimental methods alone. Our objective was to demonstrate how this quandary can be approached by a mathematical model of murine hematopoietic cell regulation (Wichmann and Loeffler 1985). The model is particularly suitable for addressing these problems since it allows one to simulate various toxicity scenarios with well defined parameters, such as cell destruction rates. With this model, discrimination between different factors responsible for the (measurable) biological changes becomes possible as shown previously for irradiation and benzene intoxication (Loeffler et al. 1985; Scheding et al. 1992).

Materials and methods

Standard model and definitions

The mathematical model is schematically summarized in Fig. 1. It is a combination of a stem cell (Wichmann and Loeffler 1985) and a mature erythropoiesis model (Loeffler et al. 1989). An additional compartment for granulocytes has been added with humoral feedback from bone marrow and blood granulocytes to CFU-GM.

Briefly, the mathematical description is based on compartments each of which comprises a defined stage of cell differentiation. Compartments are characterized by a transit time "T", a cell cycling activity "a" and either an amplification coefficient "Z" (in non-self-renewing compartments) or a self-renewal probability "p". Changes in a compartment size Y with time t are described by ordinary differential equations of type:

$$dY/dt = C^{in} \times Z - a \times Y/T$$

with C^{in} representing the cell input rate from the preceding compartment.

The model parameters either are taken directly from the literature or are fixed in the course of simulating various experiments (Wichmann and Loeffler 1985; Wichmann et al. 1988; Loeffler et al. 1989).

Control processes

The regulation of hematopoiesis is governed by three interrelated feedback loops: autoregulation of stem cells (feedback I), intramedullary feedback (feedback II) and feedback from mature cells to progenitors and precursors (feedback III).

Stem cell (CFU-S) regulation. Two distinct properties of stem cells are regulated via feedback loops I and II; namely, their cycling activity and their self-renewal. The first parameter is defined as the fraction of cells in active cell cycle (a_{CFU-S}). It determines the turnover rate of stem and thus the rate of cell production. Self-renewal is defined as the property of stem cells to maintain, after cell division, the same characteristics as the cells of origin. It is quantified by the self-renewal probability "p_{CFU-S}". A reduction in CFU-S numbers increases self-renewal and cycling (feedback I), a lack of differentiated cells stimulates stem cell cycling but decreases p_{CFU-S} (feedback II).

Regulation of committed erythropoietic and granulopoietic cells. The model assumptions on erythropoietic and granulopoietic regulation have been described in detail elsewhere (Loeffler et al. 1989; Schmitz et al. 1990). Briefly, three porperties of committed cells are regulated:

1. Variable cell cycling activities are assumed for BFU-E and CFU-GM. Decreases in CFU-S and/or progenitors and precursors of both cell lines increase the cycling activities a_{BFU-E} and a_{CFU-GM} (feedback II);
2. The proliferating erythroid precursor's transit time (T_{PEP}) depends on erythropoietin (EPO) such that high levels of EPO induce a shortening of T_{PEP};
3. Numbers of cell divisions in CFU-E and proliferating erythropoietic precursors (PEP) are controlled by EPO and in CFU-GM by CSF (colony stimulating factor(s)) (feedback III).

Stimulation of benzo[a]pyrene toxicity and identification of target cells

The hematotoxic effect of BaP is modeled by subtracting a relative fraction of cells per time from those compartments that are assumed to be targeted by BaP. Mathematically, this leads to the following equation:

$$dY_i/dt = C_i^{in} \times Z_i - a_i \times Y_i/T_i - k_i \times Y_i$$

with the loss coefficient k_i quantifying the cell loss per hour in the affected compartment "i". BaP targets, i.e. those cell stages that are affected by BaP metabolites, are identified by means of "time-curve analysis" (Scheding et al. 1992). Briefly, model time curves are created by running computer simulations with different assumptions about certain cell stages. A possible example would be that BaP destroys 3% of CFU-S per hour but spares all other cell stages. This scenario would lead to loss coefficients of $k_{CFU-S} = 0.03\ h^{-1}$ for CFU-S and $k = 0.0\ h^{-1}$ for the other compartments. Simulations of this kind yield model curves for every cell stage that can be directly compared to the experimental data with respect to the time course and extent of changes. Analysis starts with the simplest scenario, i.e. assuming that only a single cell stage is affected by BaP. A continuous broadening of the assumptions is made until a reproduction of the experimental data is achieved. The decision as to whether or not the model curve fits the experimental data is obtained by visual inspection. For example, in Fig. 2*a*, curves 2, 3 and 4 adequately reproduce the data for CFU-S while curve 1 does not.

Model results

As described in the introduction, experimental data showed that CFU-S, erythropoietic and granulopoietic progenitors and precursors were markedly reduced in D2 mice by 125 mg/kg BaP. To a lesser extent, CFU-S and erythro-

poietic cells were also reduced in BDF_1 mice. The latter, however, did not show a decrease of granulopoietic bone marrow cells. This basic data pattern therefore represented the criteria which the model simulation and assumptions had to meet. Special emphasis was put on the reproduction of the differential effect of BaP on the granulopoietic series (severe reduction of D2 and no reduction of BDF_1 granulopoietic cells).

The model analysis started with the simplest assumption, i.e. that only the cells of a single cell stage were destroyed by BaP. Although a reproduction of the data on that particular cell stage and its progenies was always possible by adequate adjustment of the loss coefficient, a reasonable fit of the entire data set was not possible. For example, the assumption that BaP affected only CFU-S led to an appropriate decrease of stem cell numbers; however, this decrease was by no means sufficient to reduce erythropoietic grogenitors and precursors to the experimentally observed levels. Extending the assumptions to several cell stages of any one cell lineage being affected did not reproduce the data either. An example for scenarios like this would be that BaP destroyed erythropoietic cells but not stem and granulopoietic cells.

We then went on to assume that more than one cell lineage was affected by BaP. Reproduction of the data was obtained by assuming that all proliferating cell stages, i.e. CFU-S, proliferating erythropoietic and granulopoietic progenitors and precursors, were targets of BaP. It was sufficient to assume that cells of any one cell lineage were affected to the same degree. Thus, only three loss coefficients $k_{CFU\text{-}S}$, k_E and k_G were needed to quantify the extent of damage.

The considerable reduction of erythropoietic cells in D2 and BDF_1 mice exposed to 125 mg/kg BaP could be reproduced only by assuming severe damage to the erythropoietic system quantified as 3.5% and 1.25% cell loss per hour (i.e. $k_E^{D2} = 0.035$ and $k_E^{BDF1} = 0.0125\ h^{-1}$) for D2 and BDF_1 mice, respectively. Thus, simulations were carried out assuming these k_Es while the loss coefficients for CFU-S ($k_{CFU\text{-}S}$) and granulopoietic cells (k_G) were varied. It was sufficient to assume that the loss coefficients could have only three values for each strain, i.e. $k_{CFU\text{-}S}$ and k_G could be "severe" ($1 \times k_E$), "moderate" ($0.5 \times k_E$) or "none" ($0.0 \times k_E$), corresponding to cell destruction rates of 3.5%, 1.25% ("severe"); 1.75%, 0.625% ("moderate"); and 0% ("none") for D2 and BDF_1 mice, respectively. These three factors generated nine different loss factor combinations ("toxicity patterns") that were tested for each strain. Model toxicity patterns assuming either severe or no damage to proliferating granulopoietic cells and/or no damage to CFU-S, resulted in considerable differences with the data. Only two combinations (representing severe damage to proliferating erythropoietic cells, moderate damage to granulopoietic cells and either moderate or severe damage to CFU-S) led to an adequate fit of the experimental data of both D2 and BDF_1 mice.

Figures 2 (BDF_1 model curves and data) and 3 (DBA/2 model curves and data) illustrate the fit of some model toxicity patterns and their corresponding model time curves with the experimental data: data for BDF_1 mice (Fig. 2) were well reproduced by model curves 2 and 3.

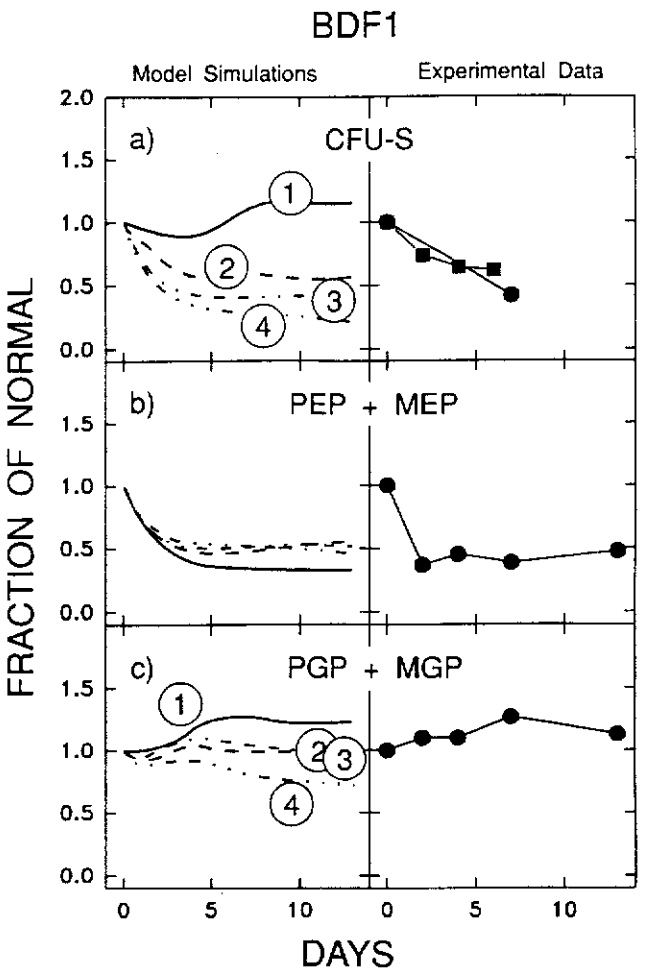

Fig. 2. Comparison of model curves (left column) with experimental data (right column) for BDF_1 mice exposed to a daily oral dose of 125 g/kg BaP. All model simulations were calculated based on the assumption that erythropoiesis is severely affected ("severe" damage, $k_E = 0.0175\ h^{-1}$). Loss coefficients and corresponding model curves were: (1) $k_{CFU\text{-}S} = k_G = 0.0\ h^{-1}$; (2) $k_{CFU\text{-}S} = k_G = 0.5 \times k_E$; (3) $k_{CFU\text{-}S} = k_E$; $k_G = 0.5 \times k_E$; (4) $k_{CFU\text{-}S} = k_E = k_G$; (5) $k_{CFU\text{-}S} = k_E$, $k_G = 0.0\ h^{-1}$ (not shown in Fig. 2). Experimental data by Anselstetter and Heimpel (1986) (●), and Anselstetter (unpublished data) (■)

They were calculated based on the assumption that granulopoietic cells were moderately damaged, whereas stem cells were moderately (curve 2) or severely (curve 3) affected. In contrast, curve 1 (no damage to stem and granulopoietic cells) predicted an increase in BDF_1-CFU-S (Fig. 2*a*), whereas the experimental data showed a significant reduction. The assumption of severe damage to both stem cells and granulopoietic cells (curve 4) led to model curves that were inconsistent with the granulopoietic bone marrow cells (PGP+MGP; Fig. 2*c*). As seen in the case of BDF_1 mice, model curves 2 and 3 also reproduced the data for D2 mice well (Fig. 3), but curve 1 showed an increase in CFU-S (Fig. 3*a*) that contrasted with the experimental data. Furthermore, curve 1 increased for granulopoietic bone marrow cells (Fig. 3*c*), whereas the experimental data clearly showed a significant reduction. Curve 5 (severe damage to stem cells and no damage to granulopoietic cells) predicted an initial increase of granulopoietic bone marrow cells rather than the decrease that was measured experimentally (Fig. 3*c*).

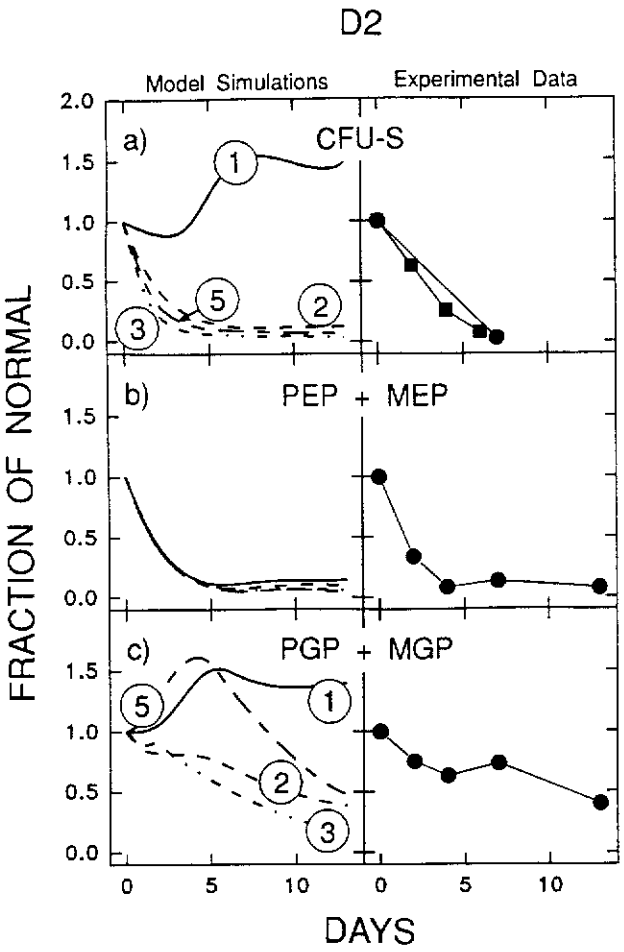

Fig. 3. Comparison of model curves (*left column*) with experimental data (*right column*) for D2 mice exposed to a daily oral dose of 125 mg/kg BaP. All model simulations were calculated based on the assumption that erythropoiesis is severely affected ("severe" damage, $k_E = 0.035\ h^{-1}$). Loss coefficients and corresponding model curves: (1) $k_{CFU\text{-}S} = k_G = 0.0\ h^{-1}$; (2) $k_{CFU\text{-}S} = k_G = 0.5 \times k_E$; (3) $k_{CFU\text{-}S} = k_E$; $k_G = 0.5 \times k_E$; (4) $k_{CFU\text{-}S} = k_E = k_G$ (not shown in this figure); (5) $k_{CFU\text{-}S} = k_E$, $k_G = 0.0\ h^{-1}$. Experimental data by Anselstetter and Heimpel (1986) (●), and Anselstetter (unpublished data) (■)

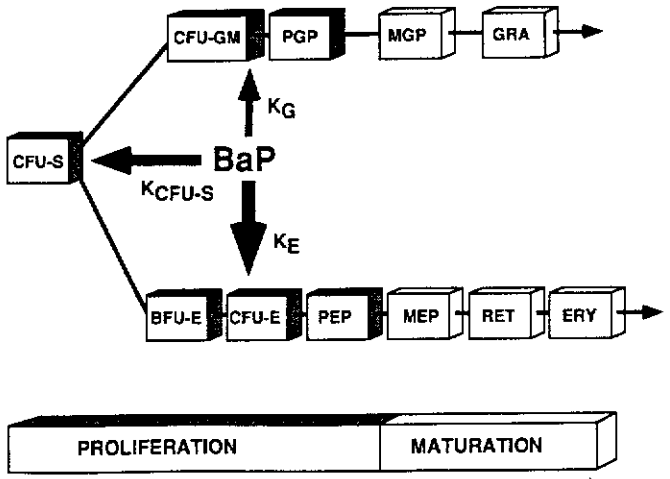

Fig. 4. Model view of benzo[a]pyrene (*BaP*) hematotoxicity. BaP affected all proliferating cell stages (*hatched area*) with loss coefficients $k_{CFU\text{-}S}$, k_E, and k_G quantifying the damage in CFU-S ($k_{CFU\text{-}S}$), proliferating erythropoietic (k_E) and granulopoietic cells (k_G). Erythropoietic cells were the most susceptible to BaP, granulopoietic cells were half as susceptible as eryhropoietic cells, and the susceptibility of stem cells ranged between that of eryhtropoietic and granulopoietic cells. This damage pattern was the same for D2 as well as BDF_1 mice. Cell destruction rates were about 3-fold higher for D2 than BDR_1 mice

Figure 4 summarizes the results of the analysis: experimental data for both strains could be simulated assuming identical toxicity patterns with BaP metabolites affecting proliferating hematopoietic cells. Within this group, erythropoietic cells were the most susceptible, granulopoietic cells were half as susceptible as erythropoietic cells and the susceptibility of stem cells ranged between that of erythropoietic and granulopoietic cells. However, loss coefficients for D2 mice were about threefold higher than those of BDF_1 mice, indicating a quantitative difference in susceptibility between both of these strains.

Discussion

A mathematical model of murine hematopoiesis was applied to analyze the hematotoxic effects of in-vivo benzo[a]pyrene exposure in BDF_1 and D2 mice. By comparison of theoretical and experimental curves with respect to the time course of toxicity, target cell stages for BaP-induced toxicity were identified and damage quantified for both strains.

The mathematical model analysis identified the proliferating hematopoietic cells, i.e. CFU-S progenitors and proliferating precursors, as the target of BaP. This finding indicates that BaP preferably killed cells that are capable of cell division. Among the proliferating cells, erythropoietic cells were found to be the most susceptible with respect to BaP toxicity; damage to CFU-S ranged between that of erythropoietic and granulopoietic cells.

These findings corresponded with the conclusions that can be drawn directly from the experimental measurements. Beyound that, however, model analysis enabled the quantification of cell losses. Furthermore, considering only the experimental data, one might conjecture that although all hematopoietic cell lines in D2 mice were affected, granulopoiesis in BDF_1 mice was not damaged by BaP. Here, the model analysis was useful since it considered the interaction of the granulopoietic lineage with the stem cells and the erythropoietic lineage as well as with hematopoietic regulation. It demonstrated that a toxic effect on granulopoiesis in BDF_1 mice is likely since the experimental data could be reproduced only by assuming moderate damage to granulopoietic cells. Experimental data reflected the net changes in certain cell stages; therefore, clear reduction of cell numbers were observable only if BaP-induced cell losses exceeded exposure-triggered regulatory cell production increases.

Data for both strains could be reproduced on the basis of an identical toxicity pattern, i.e. the ratio of loss factors $k_{CFU\text{-}S}$ to k_E and k_G to k_E was identical for D2 and BDF_1 mice. This indicated that the difference between the two strains was quantitative (e.g. resulting from different concentrations of toxic metabolites). Model analysis showed that D2 loss factors were about three times higher than

BDF_1 loss factors, in turn supporting the conclusion that D2 mice were about threefold more susceptible to the hematopoietic effects of BaP than BDF_1 mice.

Several factors could be involved in the observed strain differences. For example, differences in Cyp1a1-dependent metabolism of BaP due to Ah locus polymorphism are an important consideration (reviewed in Nebert 1989 and Nebert 1991). Briefly, the Ah locus encodes the Ah receptor which regulates the two P450I genes (Cyp1a1, Cyp1a2). Ah-responsive mice show a marked Cyp1a1 induction response when exposed to polycyclic aromatic hydrocarbons, whereas non-responsive mice lack this inducibility. The difference in BaP bone marrow toxicity between responsive and non-responsive mice was ascribed to Ah-responsive mice exhibiting a more effective first pass elimination (Nebert et al. 1977; Nebert et al. 1980; Legraverend et al. 1983). Over a 12-day BaP exposure period, Ah-responsive strains developed, on the average, about three times as much Cyp1a1 activity as did Ah non-responsive mice and covalent binding of BaP metabolites to bone marrow was 5 times lower for the Ah-responsive mice than for the non-responsive mice (Nebert et al. 1977, 1980). These findings of a 3 to 5-fold Ah-dependent difference corresponded well with the threefold difference identified by the model. The data analyzed in this report, however, are derived from two strains of mice (D2 and BDF_1) that, beside the Ah locus difference, differ in numerous other aspects; therefore, there might be other factors that potentially may influence the hematopoietic changes.

Twerdok et al. (1992) recently suggested that the difference in bone marrow toxicity between DBA/2 and C57Bl/6 mice may be related to their ability to bioactivate xenobiotics through oxidant dependent mechanisms. They reported a two-fold enhancement of oxidant-dependent chemiluminescence produced by BaP-diol in stimulated neutrophilic cells from DBA/2 mice as compared to cells from C57Bl/6 mice.

Model analysis cannot be used to determine whether Cyp1a1 and/or oxidant dependent metabolism are responsible for BaP hematotoxicity and the observed strain difference. Nevertheless, the model has allowed us to quantify the overall difference between the different strains and the model results fell within the range of the experimental data.

Besides being used to quantify observed strain difference, model analysis showed that differences exist among the different hematopoietic cell types within the same strain. Thus, differences in metabolism may exist between pluripotent stem, granulopoietic and erythropoietic cells. To our knowledge, no data exist that address this aspect and, clearly, it is a potential area for further investigation.

In summary, this study has demonstrated how a mathematical model can be applied to address questions that are not answerable by experimental methods alone. The model has proved to be an efficient tool for the analysis of benzo[a]pyrene-induced hematotoxicity.

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