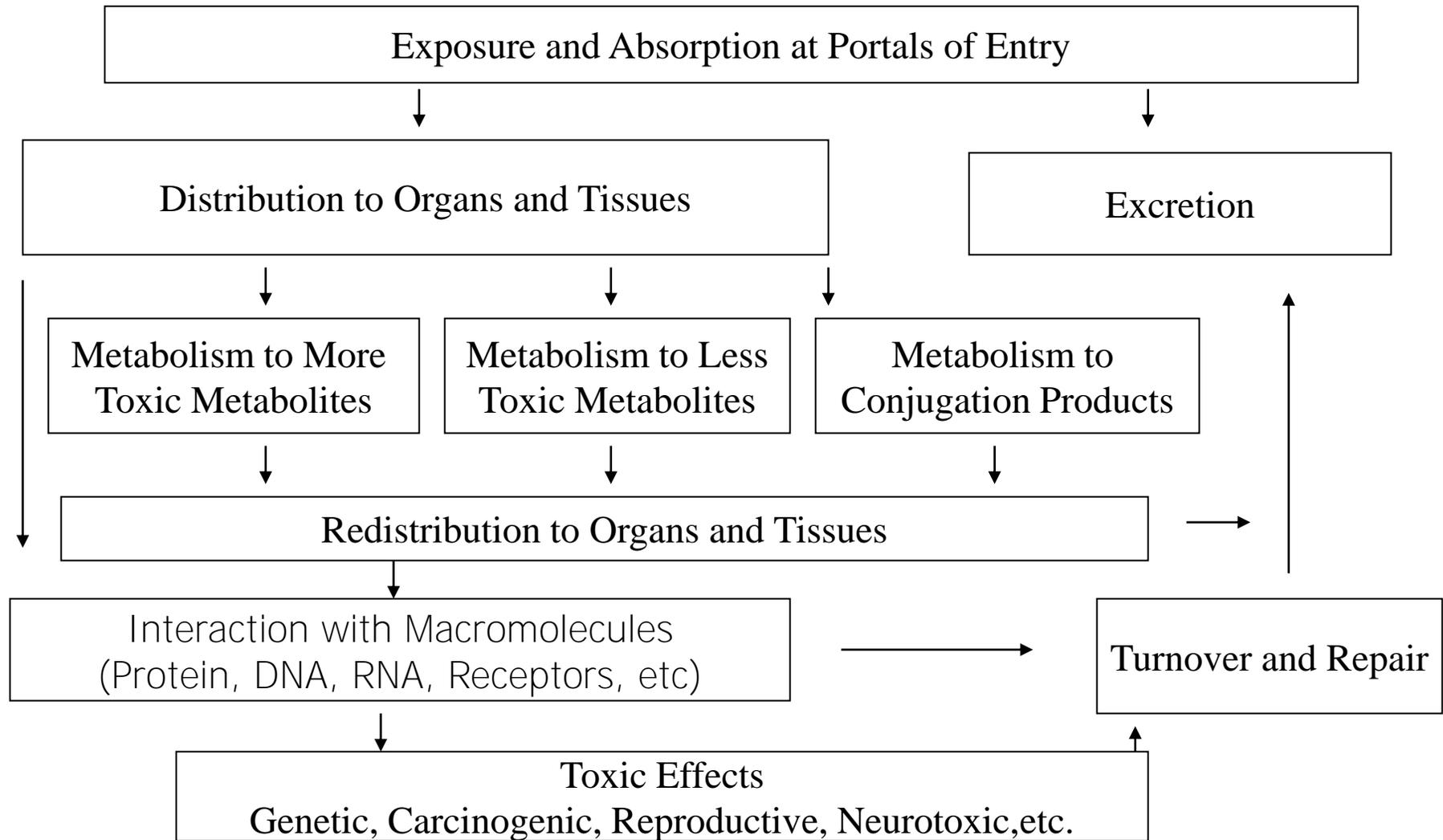


Ethylbenzene

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**Question – Are ethylbenzene-
caused lung tumors in mice of
relevance in human health risk
analysis?**



Importance of the Cascade Concept of Toxic Action

Since these steps may be reversible or irreversible, may represent alternate pathways, knowledge of each step is critical to understanding of species differences and the results of PB/PK studies.

Human health risk analysis ultimately depends on this knowledge.

Questions and answers have already been set forth for styrene.

At this point the next questions are:

1. Is ethylbenzene relevant to human health;
2. Is ethylbenzene important to human health.

To answer these questions we need to address potency, exposure and epidemiology as well as addressing the question of general relevance over and above the question of ethylbenzene-caused lung tumors in mice.

**Ethylbenzene – caused lung tumors. Important?
Occur only in males and at high doses (750 ppm)
c. 20X less potent than styrene.**

Ethylbenzene – relevant?

**Broad general exposure (usually as a complex mixture) via air
and water both to the general public but
particularly in the occupational setting.**

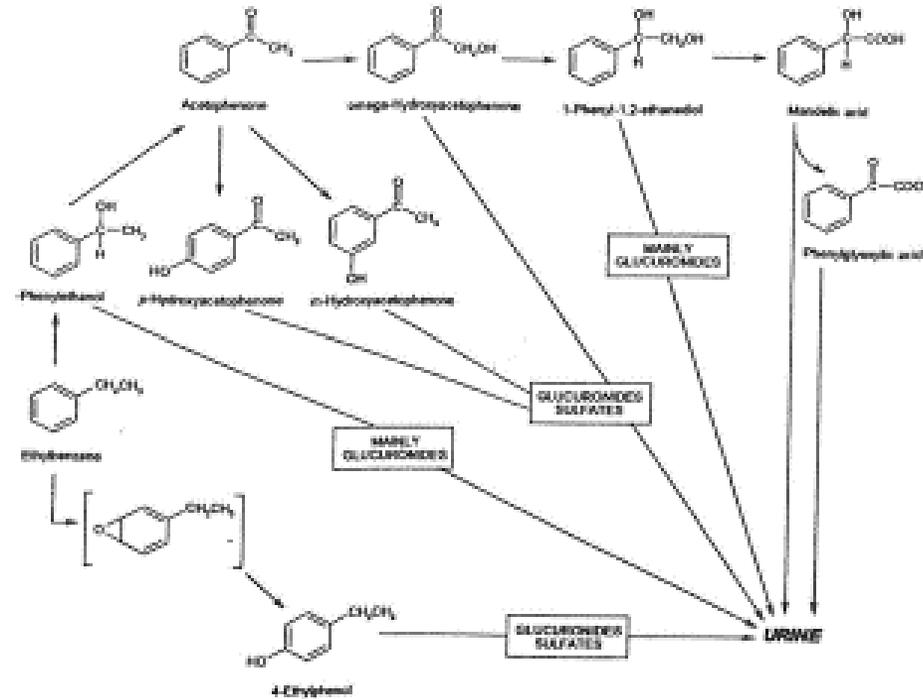
Ethylbenzene - general relevance

(Insert information on carcinogenesis in several species and several cancer types)

	Lung	Liver	Kidney	Testicles
Male mice	(750)			
Female mice		(750)		
Male rats			(750)	(750)
Female rats			(750)	

Inactive at 250 ppm but dose-response curve inadequate

Figure 3-3. Metabolic Scheme for Ethylbenzene In Humans



Source: Ergatrom et al. 1984

Metabolism of ethylbenzene

Ethylbenzene has been shown to induce CYPs 2E1, 2B1 and 2B2 in rats, induction in mice does not appear to have been studied.

1-phenylethanol – inactive – CYP2E1

2- and 4-hydroxyethylbenzene – 4 active, 2?

Some evidence, based on inhibition studies, that CYP2E1 may produce reactive metabolites

PB/PK data base

Most kinetic models involve ethylbenzene as a component of complex mixtures and are inadequate for detailed analysis. A relatively recent conclusion “while the same mechanistic issues may apply for ethylbenzene as for other mouse lung tumor agents they are not reflected in the modeling literature.” appears reasonable. One study on metabolism in the mouse lung is not detailed enough to distinguish mice from other species.

CYP2F2 produces reactive (protein-binding) metabolites in mouse liver and lung, particularly lung.

CYP2F1 is inducible in human lung cell lines.

A cautionary note (1)

While the CYP2F1/2F2 hypothesis is certainly the most probable, nevertheless, the authors (Cruzan et al., 2009) state “--- it is unlikely (emphasis mine) that metabolism by CYP2F1 would produce levels of cytotoxic metabolites in human lungs sufficient to result in lung cytotoxic responses and thus tumors.”

A cautionary note (2)

Consider the following scenario:

- 1. A human exposed to high levels of ethylbenzene as part of a complex mixture.**
- 2. CYP2F1 is known to be inducible by xenobiotics.**
- 3. This individual is at the high end of human variation for constitutive expression of CYP2F1.**
- 4. CYP2F1 level is further increased by induction.**
- 5. Individual is at the low end of human variation for expression of Phase II conjugating enzymes.**

A cautionary note (3)

While this situation would in all likelihood be rare, if it did occur would “unlikely” become “possible” or in the worst case scenario, “probable”.

Ethylbenzene – Further studies to assess relevance and importance.

- 1. Human v. mouse cell lines – avoids complications of extra-pulmonary metabolism and permits detailed dose-response, time course and inhibition studies.**
- 2. KO/KI transgenics, including humanized mice**
- 3. PB/PK**

Ethylbenzene – Summary and Conclusions

1. All aspects of the data base are too inadequate for definitive judgments to be made.
2. Ethylbenzene is a lung tumorigen in male mice.
3. If the CYP2F2/2F1 hypothesis is correct it may not be relevant to humans.
4. If CYP2F2/2F1 hypothesis is correct but not adequate it will be relevant to humans.
5. As the cause of several cancers types in several organs of both rats and mice it is relevant as a human toxicant, but not necessarily a human lung toxicant.
6. On grounds of potency relative to exposure may be relevant but not important (i.e., low priority).

Ethylbenzene – Selected References

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