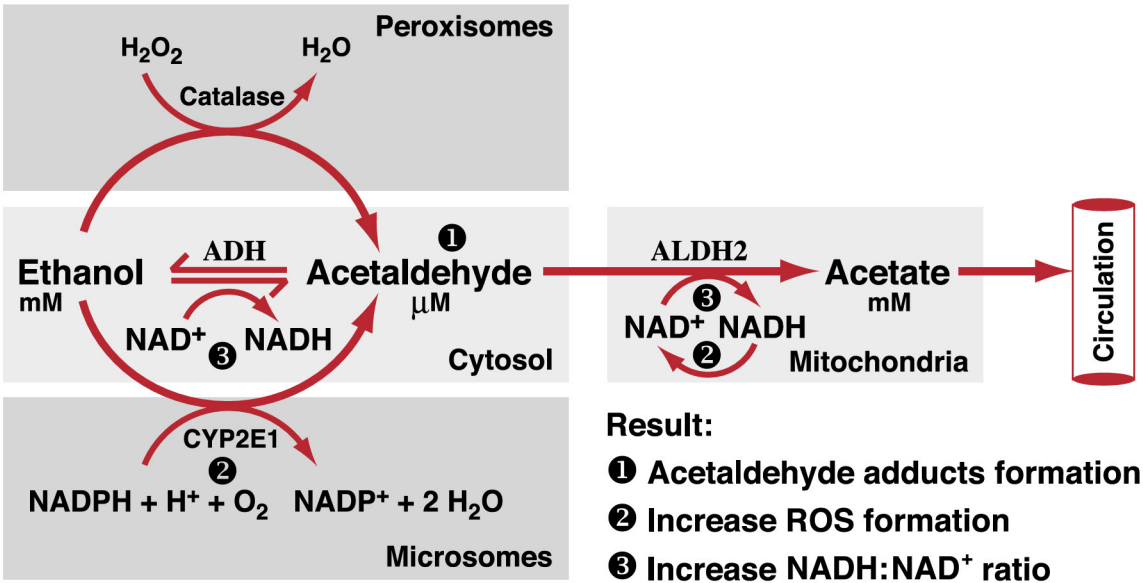

Figure 1 Oxidative pathways of alcohol metabolism. The enzymes alcohol dehydrogenase (ADH), cytochrome P450 2E1 (CYP2E1), and catalase all contribute to oxidative metabolism of alcohol. ADH, present in the fluid of the cell (i.e., cytosol), converts alcohol (i.e., ethanol) to acetaldehyde. This reaction involves an intermediate carrier of electrons, nicotinamide adenine dinucleotide (NAD^+), which is reduced by two electrons to form NADH. Catalase, located in cell bodies called peroxisomes, requires hydrogen peroxide (H_2O_2) to oxidize alcohol. CYP2E1, present predominantly in the cell's microsomes, assumes an important role in metabolizing ethanol to acetaldehyde at elevated ethanol concentrations. Acetaldehyde is metabolized mainly by aldehyde dehydrogenase 2 (ALDH2) in the mitochondria to form acetate and NADH. ROS, reactive oxygen species.

Table 1 Human Alcohol Dehydrogenase (ADH) Isozymes

Class	Gene Nomenclature New	Gene Nomenclature Former	Protein	K_m mM	V_{max} min^{-1}	Tissue
I	*ADH1A*	*ADH1*	α	4.0	30	Liver
	*ADH1B*1*	*ADH2*1*	β_1	0.05	4	Liver, Lung
	*ADH1B*2*	*ADH2*2*	β_2	0.9	350	
	*ADH1B*3*	*ADH2*3*	β_3	40.0	300	
	*ADH1C*1*	*ADH3*1*	γ_1	1.0	90	Liver, Stomach
	*ADH1C*2*	*ADH3*2*	γ_2	0.6	40	
II	*ADH4*	*ADH4*	π	30.0	20	Liver, Cornea
III	*ADH5*	*ADH5*	χ	>1,000	100	Most Tissues
IV	*ADH7*	*ADH7*	$\sigma(\mu)$	30.0	1,800	Stomach
V	*ADH6*	*ADH6*		?	?	Liver, Stomach

NOTE: The *ADH1B* and *ADH1C* genes have several variants with differing levels of enzymatic activity. K_m is a measurement used to describe the activity of an enzyme. It describes the concentration of the substance upon which an enzyme acts that permits half the maximal rate of reaction. It is expressed in units of concentration. V_{max} is a measure of how fast an enzyme can act. It is expressed in units of product formed per time.

Cytochrome P450. The cytochrome P450 isozymes, including CYP2E1, 1A2, and 3A4, which are present predominantly in the microsomes, or vesicles, of a network of membranes within the cell known as the endoplasmic reticulum, also contribute to alcohol oxidation in the liver. CYP2E1 is induced by chronic alcohol consumption and assumes an important role in metabolizing ethanol to acetaldehyde at elevated ethanol concentrations (K_m = 8 to 10 mM, compared with 0.2 to 2.0 mM for hepatic ADH). In addition, CYP2E1-dependent ethanol oxidation may occur in other tissues, such as the brain, where ADH activity is low. It also produces ROS, including hydroxyethyl, superoxide anion, and hydroxyl radicals, which increase the risk of tissue damage.

Catalase. Another enzyme, catalase, located in cell bodies called peroxisomes, is capable of oxidizing ethanol in vitro in the presence of a hydrogen peroxide (H_2O_2)-generating system, such as the enzyme complex NADPH oxidase or the enzyme xanthine oxidase. Quantitatively, however, this is considered a minor pathway of alcohol oxidation, except in the fasted state (Handler and Thurman 1990). Chronic

Products of Oxidative Metabolism of Alcohol

Acetaldehyde and acetate, produced from the oxidative metabolism of alcohol, contribute to cell and tissue damage in various ways.

Acetaldehyde. Acetaldehyde, produced by alcohol oxidation through any of the mechanisms outlined above, is rapidly metabolized to acetate, mainly by ALDH2 (in cell bodies called mitochondria), to form acetate and NADH. NADH then is oxidized by a series of chemical reactions in the mitochondria (i.e., the mitochondrial electron transport chain, or respiratory chain). Acetaldehyde has the capacity to bind to proteins such as enzymes, microsomal proteins, and microtubules. It also forms adducts with the brain signaling chemical (i.e., neurotransmitter) dopamine to form salsolinol, which may contribute to alcohol dependence, and with DNA to form carcinogenic DNA adducts such as 1,N^2-propan-