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Experimental Evaluation of Haloalkanes and Liver Injury[1]

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Experimental Evaluation of Haloalkanes and Liver Injury. PLAA, G. L. (1988). *Fundam. Appl. Toxicol.* 10, 563–570. Potentiation of haloalkane-induced hepatotoxicity by ketones and ketogenic substances is used to illustrate questions that are raised when considering biological interactions involving toxicants. The following characteristics are considered: The effect of the potentiator (ketone or ketogenic agent) on the dose–response characteristics of the haloalkane toxicant; the recovery process of the potentiated tissue injury; dose–response characteristics of the potentiators (minimally effective dosages); correlation of the potentiation with blood levels of the potentiator (threshold concentrations). The relative specificity of the haloalkanes for interaction are discussed, as well as the potentiation of various forms of hepatic injury (acute, chronic, necrogenic, and cholestatic). Enhanced bioactivation of the haloalkane toxicant is a major mechanism of action for the potentiator; other possible contributing mechanisms, however, require consideration. Mixtures of haloalkanes, leading to enhanced liver injury, can also be potentiated by ketones.

One of the purposes of this symposium is to discuss toxicological questions that are raised when considering biological interactions. Haloalkane-induced liver injury is an area that has benefited from a considerable amount of research interest; in recent years, a number of studies are particularly helpful, since they specifically deal with interactive properties. The experimental material that will be used for illustrating various points is taken from ongoing work in our laboratory dealing with the potentiation of haloalkane-induced hepatotoxicity by ketones and ketogenic substances.

Our interest in the ketone potentiation phenomenon originated with the discovery that isopropanol potentiation of CCl_4 and $CHCl_3$ hepatotoxicity (Cornish and Adefuin, 1967; Traiger and Plaa, 1971) is actually mediated by acetone, the major metabolite of isopropanol (Traiger and Plaa, 1972; 1974). Later studies (Traiger and Bruckner, 1976; Hewitt *et al.*, 1980a; 1983c) showed that a number of aliphatic ketones found in the occupational setting possess this property as well. The chlorocyclic pesticide chlordecone, which contains a carbonyl group, is also a potent potentiator of $CHCl_3$ (Hewitt *et al.*, 1979) and CCl_4 (Curtis *et al.*, 1979). Furthermore, agents that are converted to ketones *in vivo* (ketogenic substances) or maneuvers leading to metabolic ketosis are also effective potentiators (Hewitt *et al.*, 1980b). Table 1 summarizes the list of ketone and ketogenic substances that possess these properties.

CHARACTERISTICS OF THE POTENTIATION PHENOMENON

One of the questions raised concerns the effects of the potentiator on the dose–response characteristics of the toxicant. Theo-

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TABLE 1

KETONES OR KETOGENIC SUBSTANCES KNOWN TO POTENTIATE HALOALKANE HEPATOTOXICITY

Ketones	Ketogenic substances
Acetone	Isopropanol
2-Butanone (MEK)	1,3-Butanediol
2-Pentanone (MPK)	*n*-Hexane
2-Hexanone (MnBK)	4-Methyl-2-pentanol
2,5-Hexanedione	Alloxan (diabetic state)
4-Methyl-2-pentanone (MIBK)	Streptozotocin (diabetic state)
4-Hydroxy-4-methyl-2-pentanone	
2-Heptanone (MAK)	
Chlordecone	

retically the potentiator could modify the dose–response curve three different ways. In Situation I the agent lowers the effective dose of the toxicant, but the response itself follows its normal course; the dose–response curve is shifted laterally to the left but remains parallel to the one derived in nonpotentiated animals. Situation II would be where the agent does not modify the minimally effective toxic dose, but the response to the toxicant is exaggerated; the dose–response curve does not shift laterally, but its slope is increased (the curve rotates upward). Situation III would be a combination of these two phenomena; the dose–response curve shifts laterally, but the slope increases.

Decisions regarding the control of potentiators in the environment depend largely on the effect of the agent on the dose–response relationships of the toxicant. In Situation I, the no-effect level established for the toxicant when given alone is no longer applicable when exposure to this agent occurs in the presence of the potentiator; new safe-use conditions need to be established. In Situation II, the no-effect level still applies, but the injury resulting from moderately effective levels is more severe. In Situation III, the no-effect level is no longer applicable, and the injury is more severe; new safe-use conditions need to be established.

Our data indicate that the ketones which have been studied lower the threshold toxicant level of the haloalkane required to produce hepatic injury. Thus, Situation I and possibly Situation III appear to best describe the phenomenon. With chlordecone and $CHCl_3$ (Plaa and Hewitt, 1982a), evidence of a lateral shift of the dose–response relationship was observed. However, the slope of the toxic response might also be increased (Situation III). Evidence supporting Situation II (no change in the minimally effective toxicant dosage) has not been observed. The effect of chlordecone on the hepatotoxic ED50 of $CHCl_3$ is given in Table 2. It is evident that this potentiator markedly lowers the ED50 of $CHCl_3$.

When enhanced injury results, one is interested in determining whether alterations in tissue repair are involved as this process can modify the overall duration as well as the severity of the injury. With haloalkane hepatotoxicity, repair processes are initiated rapidly and the duration is dependent on the initial severity of the injury (Charbonneau *et al.*, 1985). The design of such experiments requires that one use equitoxic conditions for such comparisons; the initial injury must comparable in both the potentiated and the nonpotentiated groups so that the recovery

TABLE 2

CHLORDECONE ON CHLOROFORM MEDIAN EFFECTIVE DOSAGES (ED50 VALUES) FOR INDUCTION OF HEPATOTOXICITY IN MALE MICE[a]

Pretreatment	ALT-ED50[b]	Potency ratio[c]	OCT-ED50[d]	Potency ratio[c]
Vehicle	43 (35–50)[e]	—	235 (184–301)	—
Chlordecone	13 (10–17)	3.2 (1.3–7.8)	28 (20–43)	8.3 (5.3–12.8)

[a] Chlordecone (50 mg/kg, po) administered 18 hr before chloroform challenge (2.5–1000 μl/kg, po). Hepatotoxicity assessed 24 hr after chloroform. Data from Plaa and Hewitt (1982a).
[b] ED50 (μl/kg) for elevation of plasma ALT activity.
[c] Vehicle ED50/chlordecone ED50.
[d] ED50 (μl/kg) for elevation of plasma OCT activity.
[e] Values in parentheses represent the 95% confidence limits.

process itself can be evaluated. This means that the response obtained in potentiated animals challenged with a *small* dose of the toxicant is compared to the response obtained in nonpotentiated animals challenged with a *larger* dose of the toxicant; the severity of the initial injury should be the same (equitoxic), while the dosages of the toxicants differ. Our results with acetone, 2-hexanone, 2,5-hexanedione (Charbonneau *et al.*, 1985), or chlordecone (Charbonneau, 1982) potentiation of CCl_4 liver injury indicate that these ketones do not affect tissue repair. The time required to resolve the damage depends on the severity of the initial damage and is comparable to the time required for repair in animals challenged with an equitoxic dose of CCl_4 administered alone (Fig. 1).

The dose–response relationships of the potentiators is also of considerable interest. In all the cases that we have studied, each ketone exhibits a reproducible dose-dependent relationship. A "noneffective dosage" (NED) and a "minimally effective dosage" (MED) can be estimated (Plaa *et al.*, 1982; Pilon *et al.* 1986a; Vézina *et al.*, 1985), depending on the exposure conditions. With acetone, such values were established for both the oral and inhalation route of administration (Charbonneau *et al.* 1986a). Furthermore, with 1,3-butanediol, a ketogenic agent, the severity of the potentiation phenomenon correlates (Pilon *et al.*, 1986a) with total ketone bodies resulting from the pretreatment (Fig. 2). An interesting finding is that 2-hexanone also results in the appearance of circulating ketone bodies (Pilon *et al.*, 1986b).

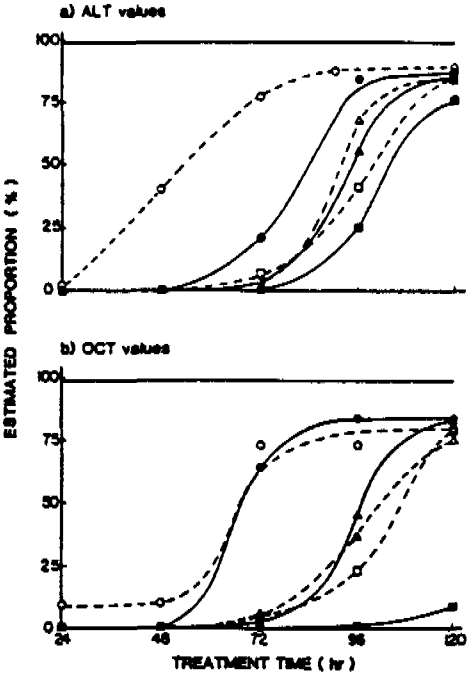

FIG. 1. Effect of ketone potentiation on the rate of recovery of CCl_4 hepatotoxicity. Groups of rats were treated with three different single dosages of CCl_4 [(○) 0.1 ml/kg, (△) 0.75 ml/kg, or (□) 1.0 ml/kg, po] and the percentage of animals exhibiting liver injury (elevation of plasma ALT or OCT activity) assessed 24–120 hr later. Other groups of rats were treated (15 mmol/kg, po) with (●) *n*-hexane, (▲) 2-hexanone, or (■) 2,5-hexanedione 18 hr before CCl_4 challenge (0.1 ml/kg, po); the percentage of animals exhibiting liver injury was assessed at the same time periods. Rate of recovery of ketone-potentiated liver injury (ALT values) was comparable to that found with an equitoxic dosage (0.75 or 1.0 ml/kg) of CCl_4 given alone. Data from Charbonneau *et al.* (1985).

TOXICANT SPECIFICITY IN THE POTENTIATION PHENOMENON

When encountering interactions the question of specificity occurs. It is important to know if several toxicants are affected or if the phenomenon is restricted to only a few agents. Table 3 summarizes the haloalkanes investigated for the ketone potentiation phenomenon (Traiger and Plaa, 1974; Plaa and Hewitt, 1982b; MacDonald *et al.*, 1982; Hewitt and Plaa, 1983). Potentiation is observed with CCl_4, $CHCl_3$, 1,1,2-trichloroethane, and 1,1-dichloroethylene. Thus, the phenomenon is not limited to CCl_4 and $CHCl_3$, but no clear haloalkane relationship is evident. There is a strong suggestion that weak hepatotoxic chlorinated alkanes are not converted into potent hepatotoxicants by a previous exposure to ketones. With the brominated derivatives, however, this conclusion is

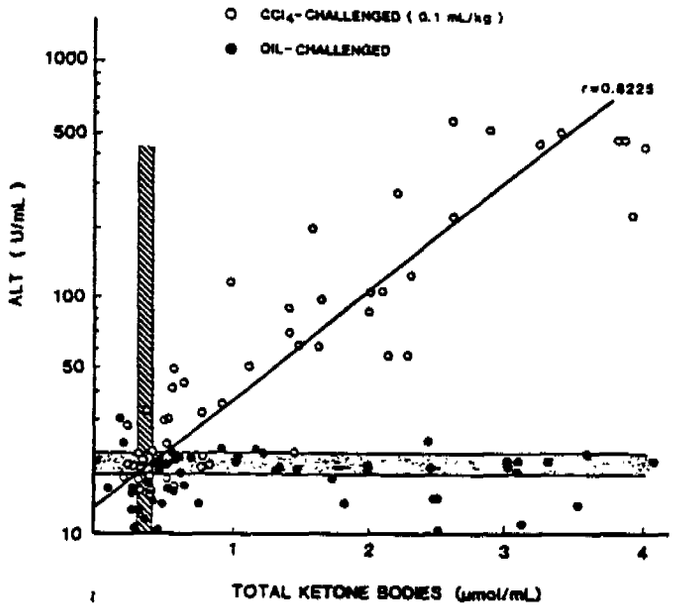

FIG. 2. Correlation between severity of potentiated CCl_4-induced hepatotoxicity and plasma total ketone body concentrations. Rats were given 1,3-butanediol (0.1–9.0% in drinking water) for 8 days. On Day 7, they were challenged with CCl_4 (0.1 ml/kg, ip). Liver injury (elevation of plasma ALT activity) and ketone body concentrations were assessed 24 hr later. Vertical hatched area represents region of normal ketone body values in control rats. Horizontal shaded area represents region of normal plasma ALT activity for control rats. Data from Pilon *et al.* (1986a).

not supported (Plaa and Hewitt, 1982b; Hewitt *et al.*, 1983d). Both acetone and chlordecone potentiation results in severe hepatotoxic responses when rats are challenged with dibromochloromethane or bromodichloromethane (Table 4); even bromoform is mildly potentiated by repetitive doses of chlordecone (Plaa and Hewitt, 1982b). The apparent difference between chlorinated and brominated analogues, when subjected to ketone treatment, requires further investigation.

TABLE 3

HALOALKANES TESTED FOR POTENTIATION BY KETONES OR KETOGENIC SUBSTANCES

Haloalkanes potentiated	Haloalkanes not potentiated
Carbon tetrachloride	1,1,1-Trichloroethane
Chloroform	1,1,2,2-Tetrachloroethane
1,1,2-Trichloroethane	Trichloroethylene (?)
1,1-Dichloroethylene	Tetrachloroethylene
Bromoform	
Bromodichloromethane	
Dibromochloromethane	

MECHANISMS OF ACTION

A cardinal consideration in interaction studies is the mechanism(s) of action involved. Such knowledge permits predictions on conditions where the interaction might be observed. With CCl_4 and $CHCl_3$, it is clear that these agents are activated by cytochrome *P*-450 to reactive toxic metabolites, which are responsible for the liver injury. Enhanced biotransformation of CCl_4 and $CHCl_3$ by acetone, 2-hexanone, 2-butanone, and chlordecone occur both *in vivo* and *in vitro* (Sipes *et*

TABLE 4

ACETONE AND CHLORDECONE POTENTIATION OF BROMOMETHANE-INDUCED HEPATOTOXICITY[a]

Pretreatment	Challenge[b]	ALT activity	OCT activity
Vehicle	$BrCHCl_2$	206	2.16
Acetone	$BrCHCl_2$	4398	35.6
Vehicle	Br_2CHCl	106	1.1
Acetone	Br_2CHCl	1506	13.56
Vehicle	$BrCHCl_2$	76	—
Chlordecone	$BrCHCl_2$	2393	—
Vehicle	Br_2CHCl	42	—
Chlordecone	Br_2CHCl	888	—

[a] Ketone was given 18 hr before haloalkane challenge. Hepatotoxicity was assessed (elevation of plasma ALT or OCT activity) 24 hr after haloalkane challenge. Data from Plaa and Hewitt (1982b) and Hewitt *et al.* (1983d).

[b] With acetone (15 mmol/kg, po) pretreatment, dosage of haloalkane challenge was 0.25 ml/kg, po. With chlordecone (50 mg/kg, po) pretreatment, dosage of haloalkane was 0.50 ml/kg, po.

al., 1973; Branchflower and Pohl, 1981; Cianflone *et al.*, 1980; Hewitt *et al.*, 1983a,b). Hepatic glutathione levels, however, are not markedly affected by the ketones (Hewitt *et al.*, 1983b). Thus, enhanced bioactivation of these haloalkanes appears to be the major mechanism responsible for the potentiation phenomenon. A critical time-interval exists for each ketone, during which subsequent challenge with the haloalkane results in potentiation (Plaa and Hewitt, 1982b). During this period we observe enhanced irreversible binding of $CHCl_3$-derived ^{14}C to microsomal macromolecules (Hewitt *et al.*, 1983b). With chlordecone this is particularly dramatic as potentiation of $CHCl_3$ hepatotoxicity is still observed 20 days after pretreatment with a single dose of chlordecone; this time interval correlates (Fig. 3) with the presence of enhanced covalent binding and persistent chlordecone tissue residues (Hewitt *et al.*, 1986b).

While enhanced activation of the haloalkanes is a major mechanism of action, there are indications that other mechanisms may also be involved. With isopropanol (the precursor of acetone) potentiation, mitochondrial and lysosomal damage following CCl_4 appears more severe than that produced by a larger dose of CCl_4 given alone (Côté *et al.*, 1974). Mehendale reported (Curtis *et al.*, 1979) that the lesion observed in animals treated with chlordecone and CCl_4 differs from that seen with CCl_4 alone. Recently, we demonstrated (Hewitt *et al.*, 1986c) that chlordecone enhances $CHCl_3$-derived ^{14}C to mitochondria and that this pretreatment also enhances lysosomal fragility to osmotic stress. Thus, one needs to consider other mechanisms that might contribute to the overall potentiation phenomenon.

CORRELATION WITH BLOOD LEVELS

It is of interest to establish parameters that can be used to describe the existance of hazardous exposure conditions between potentiators and toxicants. We found that with acetone, administered orally or by inhalation, there is an excellent correlation between the peak blood concentration of acetone and the severity of the potentiated CCl_4 liver injury (Plaa *et al.*, 1982; Charbonneau *et al.*, 1986a). A threshold blood concentration exists, above which potentiation is observed. Furthermore, when one takes into consideration the threshold blood concentration, there is an excellent correlation between the adjusted area-under-curve–time (AUC) relationship and the severity of the potentiated damage (Charbonneau *et al.*, 1986a).

With 2-hexanone, the peak blood concentration 1 hr post-treatment correlates well with the administered dose (Pilon *et al.*, 1986b). However, AUC studies comparable to those performed with acetone have not been attempted. The rapid rate of biotransformation and the high lipid solubility of 2-hexanone suggest that such correlations would be far less favorable for the ketone.

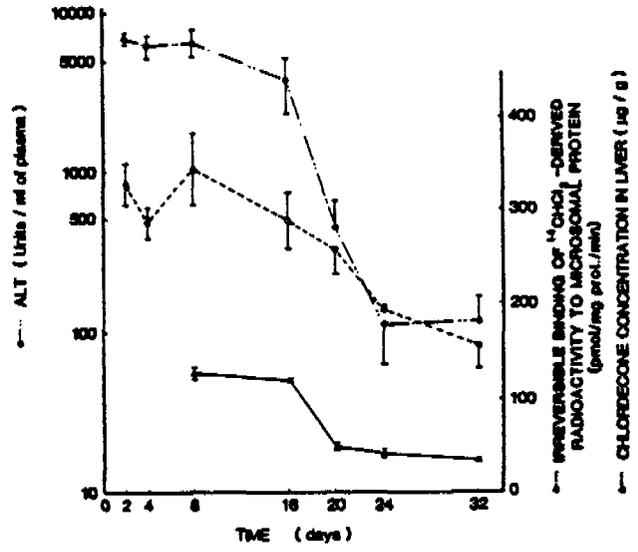

FIG. 3. Temporal relationships of chlordecone-potentiated $CHCl_3$-induced hepatotoxicity (elevated plasma ALT activity) with hepatic chlordecone concentration (µg/g liver) and *in vitro* $CHCl_3$ biotransformation rate (pmol ^{14}C/mg microsomal protein/min). Time is given in days (2–32) post-chlordecone administration (50 mg/kg, po). For the liver injury experiments, the $CHCl_3$ challenge (0.5 ml/kg, po) was administered on the day post-chlordecone treatment indicated; ALT activity was assessed 24 hr after $CHCl_3$ challenge. Data from Hewitt *et al.* (1986b).

MIXTURES OF HALOALKANES

Pessayre *et al.* (1982) demonstrated that trichloroethylene can aggravate CCl_4-induced liver injury, and that mixtures of these two haloalkanes are more potent hepatotoxicants than the agents given singly. We observed that acetone potentiates the hepatotoxicity of trichloroethylene-CCl_4 mixtures (Charbonneau *et al.*, 1986c) and has variable effects on the hepatotoxic effects of other haloalkane mixtures composed of $CHCl_3$, CCl_4, 1,1,1-trichloroethane, 1,1,2-trichloroethane, tetrachloroethylene, 1,1,2,2-tetrachloroethane, or 1,1-dichloroethylene (Charbonneau *et al.*, 1986b). An interesting finding is that with the trichloroethylene-CCl_4 mixture, the minimally effective potentiating dosage of acetone is considerably lower than that observed with CCl_4 alone. The other ketones have not been evaluated in the presence of mixtures.

OTHER FORMS OF LIVER INJURY

There is no doubt that ketones or ketogenic substances can potentiate the acute hepatonecrogenic properties of haloalkanes. Are other forms of chemically induced liver injury so affected or is the potentiation limited to the acute necrogenic response? Acetone given repetitively accelerates the appearance of cirrhosis produced by the subchronic administration of CCl_4 (Charbonneau *et al.*, 1986d). Thus, chronic lesions are also affected. Chemically induced diabetes potentiates the acute liver injury produced by thioacetamide (El-hawari and Plaa, 1983) but not acetaminophen (Price and Jollow, 1982). Thus, not all acute forms of hepatotoxicity are affected. Chlordecone enhances the cholestatic properties (diminution of bile flow) of CCl_4 (Curtis *et al.*, 1979), as does isopropanol (de Lamirande and Plaa, 1981). Acetone and 2-hexanone enhance the cholestatic proper-

ties of $CHCl_3$ (Hewitt *et al.*, 1986a). Thus, not only necrogenic hepatotoxicants are affected.

Pure cholestatic responses, in the absence of hepatocellular necrosis, are also potentiated by ketones or ketogenic substances. 1,3-Butanediol, 2-hexanone, and 4-methyl-2-pentanone enhance the diminution in bile flow observed in rats after the administration of two experimental chemical models of cholestasis—injection of taurolithocholic acid or a manganese–bilirubin combination (de Lamirande and Plaa, 1981; Plaa and Ayotte, 1985; Vézina *et al.*, 1985; Vézina and Plaa, 1986). Thus, it is clear that ketone potentiation of liver injury is not restricted to the acute hepatonecrogenic effects of haloalkanes but also involves several different forms of liver injury. The importance of these other potentiations remains to be determined.

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