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JUN 12

This appears to be the latest manuscript
of metabolic work on VCM.

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cc (FK) DAK

6/23/78

has not say + the notation
of it all, but there are
some gaps in the work for
the time being.

CHEMICALS
RESEARCH

JUN 27 1978

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RESOLUTION OF DOSE-RESPONSE TOXICITY DATA FOR CHEMICALS
REQUIRING METABOLIC ACTIVATION: EXAMPLE - VINYL CHLORIDE

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Abbreviated Title: Dose-response: Vinyl Chloride

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Resolution of dose-response toxicity data for chemicals requiring metabolic activation: Example - vinyl chloride. Gehring, P. J. Watanabe, P. G. and Park, C. N. (1977). Toxicol. Appl. Pharmacol. __, __-__. The toxicity of many chemicals results from biotransformation products formed from the chemical rather than from the chemical per se. In such cases, the incremental response may become diminishingly smaller with increasing dose or exposure because activation of the chemical to the toxic form follows apparent Michaelis-Menten rather than apparent first-order kinetics.

To illustrate this concept, rats were exposed to concentrations ranging from 1.4 to 4600 ppm vinyl chloride for 6 hours and the total amount metabolized determined. The amount metabolized followed apparent Michaelis-Menten kinetics. For rats, the logarithmic probability incidence of angiosarcoma versus the amount of vinyl chloride metabolized rather than the exposure concentration of vinyl chloride is linear. Assuming no threshold inspite of evidence to the contrary, extrapolation of the data below the range of doses causing experimentally observable responses predicted an incidence of 0.01% hepatic angiosarcoma in rats exposed to 4.6 ppm vinyl chloride. Theoretical extention of the extrapolation to humans after adjusting for metabolic and body mass differences was undertaken. The theoretical extrapolation for man exposed daily for 8 hours to 1 ppm suggests an incidence of 1.5 per 100,000,000. This theoretical incidence, although a likely

overestimate because of a less than predicted incidence in men exposed to 200 ppm and greater as well as evidence for a threshold in rats, is less than that expected to occur spontaneously. The concepts evolved from this analysis reveals why pharmacokinetics must be considered in designing toxicology experiments as well as in interpretation of the resulting data.

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There exists a great deal of uncertainty in predicting the potential response of exposure to chemicals at concentrations below those producing an experimentally discernible response. This is particularly true when the response to the chemical in question is oncogenesis. Statistical projections recommended for assessing the risk of exposure to doses of oncogenic chemicals lower than those producing an observable response include those based on logarithm probability curves (probit curves), logistic curves or linear curves (one-hit curves), (FDA Advisory Committee on Protocols for Safety Evaluation, 1971). One of the most commonly used statistical projections for risk assessment has been that promoted by Mantel and Bryan (1961) in which a logarithm probability projection with a slope of one is utilized. A flaw innate to all of these methods is that the dose-response information used to make the projection is based on the dose of chemical administered to the animal rather than the quantity of the administered dose giving rise to the response; the latter may either increase or decrease disproportionately as the administered dose is increased.

The use of high doses to reveal the chronic toxicity incurred with exposure to a chemical is a common, scientifically

defensible practice if judgment and scientific rationale are used in designing the experiments and in assessing the resulting data. However, such doses overwhelm frequently the enzymatic processes for activation of the chemical to the toxic form or for deactivation of the toxic form to an innocuous form. In this paper, it is demonstrated how the dose-dependent activation of vinyl chloride to an oncogenic product must be considered in resolving the dose-response of rats exposed via inhalation to vinyl chloride.

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METHODS

Material.

Vinyl chloride (^{14}C -labeled) was synthesized from (1,2- ^{14}C) 1,2-dichloroethane (New England Nuclear, Lots #819-221 and 819-292, 5.0 and 4.8 mCi/mole, respectively) directly prior to use (Wagner et al., 1975). Non-labeled VC (Matheson Gas Products) of 99.9% purity was mixed with the ^{14}C -material to obtain the desired specific activity.

Animals.

Male, Sprague-Dawley rats (Spartan Research Laboratory) weighing 200-250 g were used throughout the study. Food and water were provided ad libitum except during the exposure. Exposures were conducted between 9:00 a.m. and 3:00 p.m. (EST). Groups of 3-6 rats were exposed to various concentrations of ^{14}C -VC for 6 hours.

Exposure and Procedure.

The rats were exposed by inhalation under dynamic conditions in a 30 % glass inhalation chamber. The mean analytical concentrations of VC measured by gas chromatography were 1.4 ± 0.3 (SD), 9.3 ± 0.2 , 24.7 ± 1.4 , 51 ± 2 , 109 ± 23 , 250 ± 2 , 511 ± 11 , 1020 ± 13 , and 4600 ± 311 ppm. Details of this exposure and the method of analytical determinations have been reported previously (Watanabe et al., 1976a). Immediately following

the 6-hour exposure to various concentrations of ^{14}C -VC (1.4-4600 ppm) the rats were killed by a blow to the head, and the carcass was analyzed for total radioactivity (Watanabe, et al., 1976b). Previous studies have shown that only a small percentage of radioactivity (<12%) is excreted as metabolites other than ^{14}C -VC during 72 hrs following a 6 hr inhalation exposure (Watanabe et al., 1976a). The large proportion of the 12% is comprised of $^{14}\text{CO}_2$ excretion 72 hrs after exposure. Furthermore, very little urine is excreted during the exposure period. Thus, the non-volatile radioactivity determined immediately after exposure in the tissue and carcass is a good estimate of the total amount of metabolized VC.

RESULTS

Consistent with the results of previous studies (Watanabe et al., 1976a and 1976b), the metabolism of VC by rats does not increase proportionately with increasing concentrations of VC being inhaled (Table 1). The nonlinearity of the amount of VC metabolized during 6 hours of exposure to various concentrations of VC appeared to be in accordance with Michaelis-Menten kinetics as described by the equation:

$$v = \frac{V_m S}{K_m + S} \quad (1)$$

In this equation, v and V_m , are the velocity and maximum velocity respectively for the biotransformation of VC expressed as μg equivalents VC metabolized per 6 hours. S and K_m are the concentration of VC being inhaled and the Michaelis constant expressed as $\mu\text{g VC/l air}$, respectively.

To ascertain whether Michaelis-Menten kinetics were applicable, the data in Table 1 were analyzed in accordance with the linear *Woolf Augustinohorowitz* transformation of the Michaelis-Menten equation (Segel, 1976),

$$v = \frac{V_m}{K_m} \frac{S}{1 + \frac{S}{K_m}} \quad (2)$$

It can be seen from the plot (Fig. 1) that the data appear to lie along a straight line thus verifying, at least visually, the Michaelis-Menten model. V_m and K_m can be estimated by the ordinate intercept and the slope of the line or they can be estimated directly by fitting the nonlinear Michaelis-Menten model. Both procedures yield similar parameter estimates. The estimates derived by fitting the model directly are 8558 ± 1147 (SD) $\mu\text{g VC}$ metabolized and 860 ± 159 (SD) $\mu\text{g VC/l air}$ for V_m and K_m respectively.

Once a means is obtained to calculate the amount of VC metabolized by rats as a function of exposure, it is then possible to relate the untoward effects associated with VC exposure to the amount biotransformed rather than the exposure concentration of VC per se incurred by rats exposed to VC.

Maltoni and Lefemine (1975) reported the incidence of hepatic angiosarcoma in rats exposed to different concentrations of VC, 4 hours/day, 5 days/week for 12 months and subsequently held for observation until death (Table 2). Before attempting to relate these data to the amount of VC biotransformed in accordance with the Michaelis-Menten equation using the previously determined values of V_m and K_m , the value for V_m must be adjusted for the shorter exposure duration used by

Maltoni and Lefemine, 4 hours versus 6 hours. This adjustment is accomplished by multiplying V_{in} by 4/6. Thus, the amount of VC biotransformed daily by rats exposed to the various concentrations used in the experiment of Maltoni and Lefemine can be calculated from the equation:

$$v = \frac{5706 \left(\frac{\mu g}{4 \text{ hr}} \right) \cdot S \left(\frac{\mu g}{l} \right)}{860 \left(\frac{\mu g}{l} \right) + S \left(\frac{\mu g}{l} \right)} \quad (3)$$

The resulting values for v are given in Table 2.

Figure 2^a depicts a logarithm probability plot (probit plot) of the incidence of hepatic angiosarcoma observed in rats by Maltoni and Lefemine (1975) versus the amount of VC biotransformed for 4 hours of exposure, v , or the exposure concentration, S . The incidence of hepatic angiosarcoma in rats is linear with respect to $\log v$ but not $\log S$. The line drawn for $\log v$ versus tumor incidence (Figure 2) was determined by using a probit regression analysis program, and the equation relating the incidence of hepatic angiosarcoma to $\log v$ was:

$$\text{probit response} = -1.625 + 1.543 \log v \quad (4)$$

Using the foregoing equation, a projection below the levels of exposure producing an experimentally discernible response has been made (dashed line). Assuming no threshold for the induction of angiosarcoma in rats exposed to VC, the exposure concentration producing one angiosarcoma in 10,000 rats can be calculated. The probit percent representing an incidence of 0.01% is 1.28. Substitution of this value into the equation (4) yields:

$$\text{Log } v = 1.8827$$

$$v = 76.33 \text{ } \mu\text{g VC metabolized/4 hours}$$

Using equation 3, the concentration of exposure to VC needed to give this value for v is 11.66 $\mu\text{g/l}$ or 4.6 ppm (approximate 95% confidence limits obtained by substituting the upper and lower 95% confidence limits for v in equation 3 and solving for S are 0.03-8.7 ppm). Hence, exposure of rats to 4.6 ppm VC for 4 hours daily, 5 days/week for 1 year can be expected to produce one angiosarcoma per 10,000 rats if the dose-response curve remains valid at exposures less than those producing a discernible experimental response.

DISCUSSION

For many chemicals, toxicity may not be a function of exposure to the chemical per se, but rather to a biotransformation product of the chemical. Frequently, production of a toxic metabolite is dependent upon enzymatically mediated reactions which are classically described by Michaelis-Menten kinetics. Since enzymatically mediated reactions are concentration-dependent and saturable, toxicity resulting from exposures to chemicals requiring activation to a toxic form cannot be related directly to the magnitude of exposure or dose. In such a case, it is necessary to determine the amount of the chemical undergoing biotransformation as a function of dose or exposure before a meaningful dose-response relationship can be established.

There is considerable evidence that vinyl chloride requires bioactivation to produce tumors. Metabolic activation is required to induce mutations in bacteria exposed to VC (Bartsch et al., 1975; Malavielle et al., 1975; Rannug et al., 1974). Covalent binding of ^{14}C to hepatic macromolecules in rats (Matanabe et al., 1977) exposed to ^{14}C -VC also requires bioactivation. Covalent binding of electrophiles to DNA has been associated with tumorigenesis.

For vinyl chloride-induced hepatic angiosarcoma in rats, a logarithmic probability plot (probit plot) of the incidence versus the amount of vinyl chloride metabolized, v , over a range of exposures from 50 to 10,000 ppm VC gives a classical straight line, Fig. 2a. The dose-response relationship is not a straight line when plotted as a function of the exposure concentration, C (Fig. 2b). These results support further the conclusion that VC requires biotransformation to an active metabolite for tumorigenicity. Furthermore, a more reasonable evaluation of the dose-response data for vinyl chloride induced tumorigenesis requires knowledge of the amount of VC activated as a function of exposure.

After arbitrarily excluding data acquired from rats exposed to concentrations of VC exceeding 500 ppm in the experiment of Maltoni and Lefemine (1975), Schneiderman et al (1975) extrapolated the remaining data to predict an incidence of 0.01% hepatic angiosarcoma in rats exposed to 1 ppm VC. This number is reasonably close to our prediction of 4.6 ppm VC for the same incidence. If Schneiderman et al had used all of the data, a dose-response curve with an unrealistically shallow slope would have resulted and the predicted level causing 0.01% hepatic angiosarcoma would have been much smaller, on the order of 0.00001 ppm.

The concepts developed herein allow use of all of the data presented by Baltoni and Defemine (1975) to construct a dose-response curve on a scientifically defensible basis. Assuming that the resulting dose-response curve can be projected beyond the range of the experimentally discernible responses, the exposure concentration required to produce an incidence of 0.01% hepatic angiosarcoma in rats is 4.6 ppm.

Aside from interpreting toxicity data for chemicals requiring activation to a toxic form, there are some practical implications of the concepts presented herein for designing experiments to assess the toxicity, including carcinogenicity, of such chemicals. For these chemicals, increasing the concentration above the apparent K_m will produce diminishingly smaller increments in the response; no increase in the response is to be expected when the exposure concentration is 2 or 3 times K_m . Since total dose is a function of exposure time as well as concentration, it is important to determine the effect of exposure time on the response. As shown in Equation 3, the only parameter influence^d by exposure time is V_m , which is increased linearly with time. Therefore, after the concentration to which the animals are exposed becomes 2 to 3 times K_m , the amount metabolized, v , will increase linearly with increasing exposure time. For

this reason, the gradation of incidence of angiosarcoma in rats exposed to high concentrations of VC will become a function of exposure time rather than concentration. This reasoning makes it imperative that the duration of exposure as well as exposure concentration be considered in evaluating the results of epidemiological studies of people exposed to high concentrations of VC in the work environment.

Unless the dose-dependent, Michaelis-Menten type pharmacokinetic parameters are resolved prior to designing the experiment, the results may be robbed of much of their value for characterizing the dose-response function for the untoward effects observed. Thus, the current approach using the maximum tolerated dose as defined presently and fractions thereof, may be scientifically unsound if the objective is to assess the potential toxicity of exposure to much lower doses or exposures.

For some chemicals detoxification of the chemical per se or reactive metabolites formed from the chemical may also be dose-dependent and saturable leading to a build-up of toxic materials. In such cases, the incremental responses to increasing doses or exposures will become disproportionately larger rather than smaller (see Gehring and Blau, 1977).

In the foregoing analysis of the dose-response data for the induction of angiosarcoma in the rat, no threshold for the response was assumed. As indicated, extrapolation below the range of doses resulting in an observable response may overestimate the response in rats because there is evidence that detoxification of reactive metabolites of VC may occur more efficiently in rats exposed to concentrations of VC below 50 ppm (Watanabe et al 1976c). Indeed, further analysis of the data reported by Maltoni and Lefemine (1975) also provides an indication of a practical threshold. In a subsequent presentation of these data, it was revealed that the latency for the development of hepatic angiosarcoma was respectively 64, 70, 78, 81, 79 and 135 weeks for rats exposed to 10,000, 6,000, 2,500, 500, 250 and 50 ppm VC (Maltoni, 1975). These results indicate that at some low levels of exposure the time required for induction may exceed considerably the life expectancy for rats. This is consistent with the work of others suggesting that multiples of a lifetime may be required for expression of cancer in response to low doses of a carcinogen (Druckrey, 1967 and Albert and Altshuler, 1973). Thus, extrapolation of the data obtained for rats below the range of exposures causing a discernible response may be expected to overestimate the projected incidence.

The ultimate objective of a toxicological study is to develop data which can be used to assess the potential risk for man. It is worthwhile to utilize the concepts presented herein to achieve this objective realizing fully that such extrapolation is fraught with uncertainties. The basic assumptions made are:

- 1) Induction of angiosarcoma is related to the amount of reactive metabolite of VC per unit of mass.
- 2) Exposure of rats for 12 months approximates exposure of workers for their working life.
- 3) There is no threshold for the induction of angiosarcoma in either rats or man which likely overestimates the assumption of risk as discussed above.
- 4) The efficiency of the metabolic processes involved in the conversion of VC to the reactive form is proportional to the body surface area. Since data for the biotransformation of VC by man are not available, the most logical basis for translation of the animal data to man would seem to be on the basis of body surface area.

The last assumption deserves comment. There are considerable data in the literature showing that metabolism in general and other physiological parameters as well are relatable directly to the surface area of the body (see Schmidt-Nielsen, 1970; and Pinkel, 1958). For this reason, administration of biologically active chemicals to various species frequently gives an equivalent response when the dose is administered in proportion to the surface area of the body, that is dose per square meter of body surface (Pinkel, 1958). This relationship is gaining recognition in estimating the risk incurred by man from exposure to chemicals in the environment (Committee on Safe Drinking Water, National Research Council, 1977). In utilizing this relationship it must, however, be recognized that the original relationship was developed for biologically active agents. Since metabolism and other physiological processes involved in detoxification are more active in smaller animals, the dose of a biologically active chemical per unit of mass required to produce a given effect increases as the body mass decreases, while the dose per unit surface area remains relatively constant. However, for a chemical requiring activation to the biologically active toxic form, the total amount transformed will be roughly proportional to the body surface area. Since toxicity is a function of the concentration of the active form in tissue, this total amount transformed must then be normalized for mass to produce an equivalent response.

Using aforementioned rationale, the maximum velocity, V_m , for a 70 kg man can be estimated by calculation using the V_m value obtained for a 0.250 kg rat. The V_m of man for VC will be :

$$V_m \text{ (man)} = V_m \text{ (rat)} \left(\frac{1.85 \text{ sq m}}{0.045 \text{ sq m}} \right)$$

or

$$V_m \text{ (man)} = (8558 \text{ } \mu\text{g}/6 \text{ hr}) \left(\frac{1.85 \text{ sq m}}{0.045 \text{ sq m}} \right) = 351829 \text{ } \mu\text{g}/6 \text{ hr}$$

where the values 1.85 and 0.045 sq m are the body surface areas of a 70 kg man and a 0.250 kg rat, respectively (Pinkel, 1958). For an 8 hour exposure, the value is 469105 $\mu\text{g}/8 \text{ hr}$. In order to use this number to theoretically estimate the response in man using data collected in rats, the V_m for man must be adjusted to a mass equivalent to that of rats since toxicity is a function of concentration in tissue. To do this the number is divided by 70 kg/0.25 kg or 280. The resulting V_m for man on a mass equivalent basis to that of rats is 1675 $\mu\text{g}/8 \text{ hr}$. Using this value, the amount of VC transformed to a reactive form by man on a mass equivalent basis to rat is given by the equation:

$$V \text{ } \mu\text{g}/8 \text{ hr} = \frac{1675 \text{ } \mu\text{g}/8 \text{ hr} \cdot S \text{ } \mu\text{g}/\text{L}}{860 \text{ } \mu\text{g}/\text{L} + S \text{ } \mu\text{g}/\text{L}} \quad (5)$$

Using this equation, the amount of VC transformed by man on a mass equivalent basis to rats was calculated as a function of exposure concentration and the expected incidence of angiosarcoma estimated from equation 4 (Table 3).

For men exposed to greater than 200 ppm VC, the incidence of angiosarcoma has been reported to be 0.02% (Fox and Collier, 1977). Hence, the theoretical calculated incidence using data from rats exceeds that currently detected by approximately 50 fold. This may indicate that people are less sensitive than rats to the induction of angiosarcoma or it may indicate that a practical threshold for the induction of angiosarcoma had been attained. Consistent with this latter possibility is that V on a mass equivalent basis to rats for men exposed to 200 ppm is 625. This number lies below that for rats exposed to 50 ppm. As indicated previously, angiosarcoma observed in rats exposed to 50 ppm occurred only in a rat that lived 135 weeks (Maltoni 1975). Further, this rat did not die as a result of the angiosarcoma but was killed. Thus, as indicated previously, projection of the data collected in rats below the range of exposures producing an observable response may overestimate the incidence.

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Inspite of the likelihood of overestimating the incidence of angiosarcoma in rats or man, the incidence predicted for people exposed to 1 ppm, the current OSHA (Occupational Safety and Health Act) standard, is very small (1.5 per 100 million). This value which is likely an overestimate is below the expected incidence of spontaneous angiosarcoma reported to be 20 to 25 cases in the U.S. annually (Makk, et al, 1976).

In summary, it has been demonstrated that the incidence of VC induced angiosarcoma in rats is relatable not to the concentration of exposure but rather to the amount of VC biotransformed. Biotransformation of VC by rats is a dose-dependent process characterized by Michaelis-Menten type kinetics. The concepts evolved from this analysis reveals why pharmacokinetics must be considered in designing toxicology experiments as well as in interpretation of the resulting data. Having characterized the dose-response for induction of angiosarcoma in rats as a function of the amount of VC biotransformed, a theoretical estimate of the incidence expected to occur in exposed men was undertaken using the data collected in rats. For daily 8 hr exposures to 1 ppm, the predicted incidence is 1.5 in 100,000,000 which is less than that expected to occur spontaneously. This predicted

incidence is likely an over-estimate of that which will occur as a result of exposure to 1 ppm because there is some evidence for at least a practical threshold in both rats and man. There are no illusions that this estimate by extrapolation of data outside the range of doses causing experimentally observable responses and subsequently to man is without flaws. However, the rationale used represents a new approach which utilizes more logic than methods employed currently for such extrapolation.

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VVC 000003178

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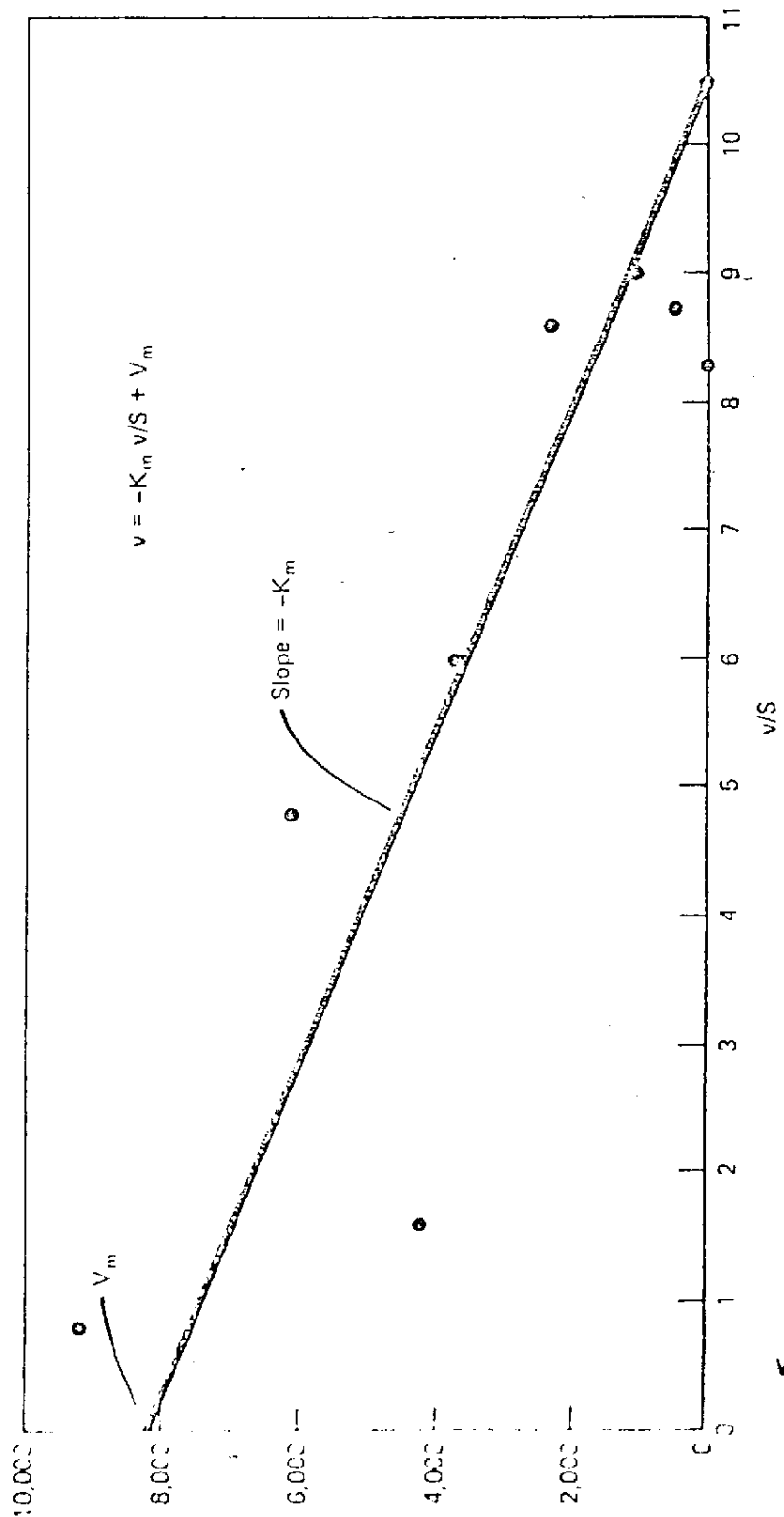
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LEGENDS

Figure 1. Metabolism of vinyl chloride analyzed in accordance with the Woolf-Augustinson-Hofstee linearized form of the Michaelis-Menten equation. Values of v and v/S were taken from Table 1. The line was fit by linear regression analysis. The correlation coefficient, R , was 0.88.

Figure 2. (a) Metabolism of vinyl chloride expressed as $\log v$ ($\frac{\mu\text{g VC metabolized}}{4 \text{ hr}}$) versus percent incidence of hepatic angiosarcoma (probability scale). (b) Exposure concentration expressed as $\log S$ (ppm) versus the percent incidence of hepatic angiosarcoma. The probit equivalents of the percent incidence are shown on the right hand ordinant. The solid line is the best fit for experimentally observed responses while the dashed line represents extrapolation below those doses producing an observable response assuming no threshold.

FIGURE 1



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FIGURE 2

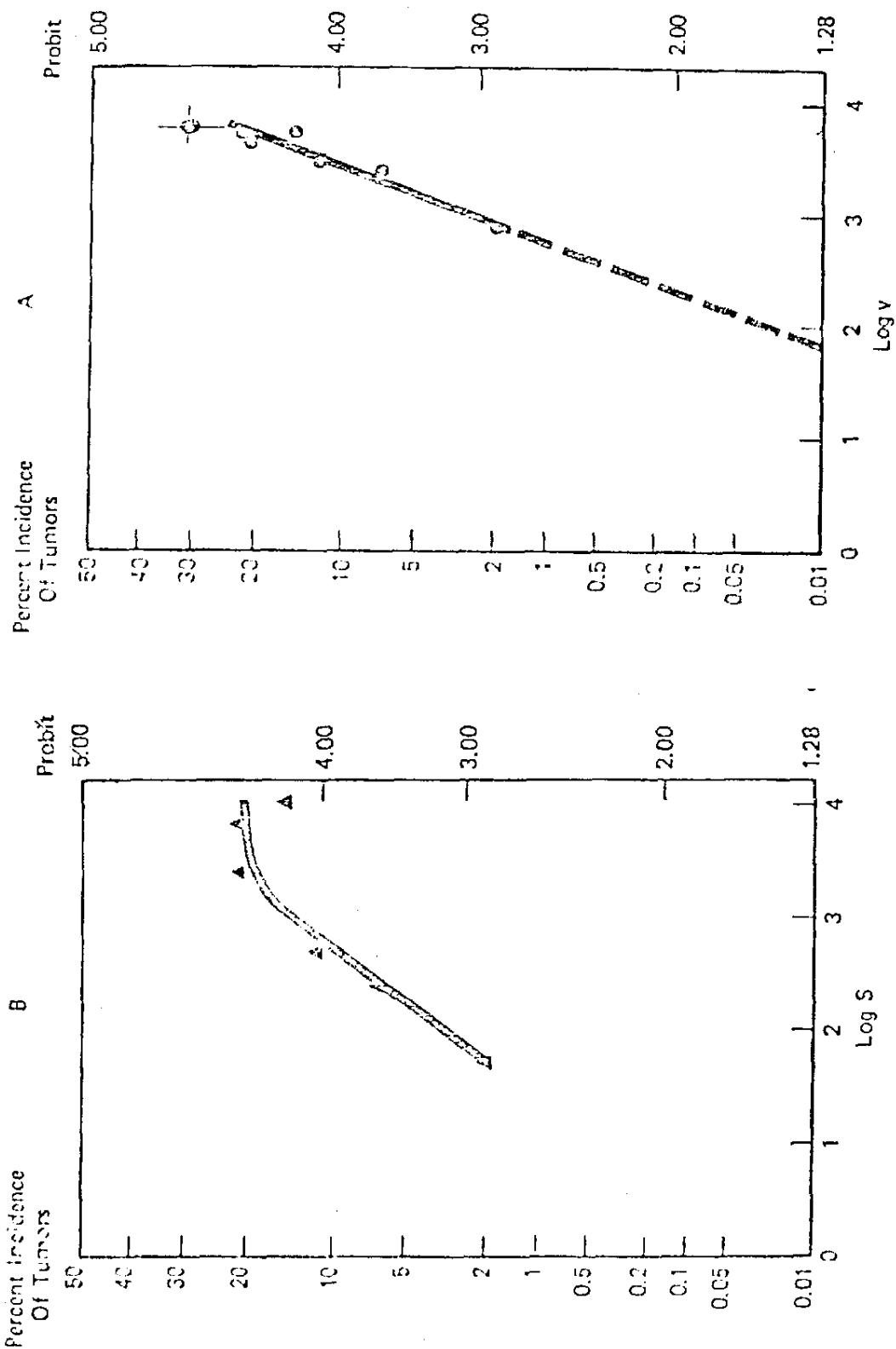


TABLE 1

Parameters for Describing the Metabolism of Inhaled Vinyl Chloride (VC) Using Michaelis-Menten Kinetics

Exposure Concentration <u>S (ppm VC)</u>	<u>S (µg VC/l air)^a</u>	<u>v µg VC metabolized^b 6 hr</u>	<u>v/S</u>
1.4	3.6	30±3 ^c	8.33
9	23.0	242±26	10.52
25	64.0	557±42	8.70
51	130.6	1181±93	9.04
109	279.0	2406±173	8.62
250	640.0	3826±345	5.98
511	1308.2	6263±355	4.79
1020	2611.2	4257±765	1.63
4600	11776.0	9255±1467	0.79

^a 1 ppm VC = 2.56 µg VC/l air

^b Determined from the total radioactivity in the carcass

^c Mean ± standard deviation

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TABLE 2

Correlation Between Exposure Concentration of Vinyl Chloride,
Metabolism and Induction of Hepatic Angiosarcoma in Rats

Exposure Concentration S (ppm VC)	S ($\mu\text{g VC}/\ell \text{ air}$) ^a	$\mu\text{g VC metabolized}$ v 4 hr	100 v 52	Percent Incidence of Hepatic Angiosarcoma ^c
5,000	46,800	2,642	5,521	15
10,000	25,600		3,742	
5,000	15,360	5,403	3,733	22
2,500	6,400	5,030	3,702	22
500	1,280	3,413	3,533	12
250	640	2,435	3,386	7
50	128	739	2,869	2

-28-

$$a \quad 1 \text{ ppm VC} = 2.56 \left(\frac{\mu\text{g VC}}{\ell \text{ air}} \right)$$

$$b \quad v_m \text{ corrected for 4 hour exposure, } 8558 \left(\frac{\mu\text{g VC metabolized}}{6 \text{ hr}} \right), \quad 4/6 = 5706 \left(\frac{\mu\text{g VC metabolized}}{4 \text{ hr}} \right)$$

$$v = \frac{5706 \left(\frac{\mu\text{g VC}}{4 \text{ hr}} \right) \cdot S (\mu\text{g}/\ell)}{860 (\mu\text{g}/\ell) + S (\mu\text{g}/\ell)}$$

^c From Maltoni and Lefemine (1975).

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TABLE 3

Theoretical Amounts of Reactive Product Formed From VC By a 70 kg Man Exposed Continuously For 8 Hours and the Corresponding Expected Incidence of Angiosarcoma as Predicted From Data Collected in Rats Assuming No Threshold

Exposure Concentration ppm	VC metabolized ^b		Log V	Probit Response ^c	Theoretical Percent Incidence of Angiosarcoma ^c
	ppm	8 hr			
200	512	625	2.79	2.68	1.02
50	128	217	2.34	1.98	0.11
5	12.8	24.6	1.39	0.52	3.74×10^{-4}
1	2.56	4.97	0.70	-0.54	1.5×10^{-6}

^a 1 ppm = 2.56 µg/l.

^b V has been calculated using the Michaelis-Menten equation after calculating the $V_{\max}$ for man from the $V_{\max}$ determined for rats. This calculation was made by assuming $V_{\max}$ is proportional to body surface area and subsequently adjusting it to a mass equivalent to that of rats.

See text.

^c The expected probit response was calculated from probit equation 3 (text). Subsequently the theoretical percent incidence of angiosarcoma was determined from the respective probit.

INDEX TERMS

Chloroethylene

Vinyl chloride

Chloroethene

Metabolism

Dose-response

VVC 000003188

22936

[4910-13]

[Airspace Docket No. 78-WE-5]

PART 71—DESIGNATION OF FEDERAL AIRWAYS, AREA LOW ROUTES, CONTROLLED AIRSPACE, AND REPORTING POINTS

PART 73—SPECIAL USE AIRSPACE

Designation of Temporary Restricted Area

AGENCY: Federal Aviation Administration (FAA), DOT.

ACTION: Final rule.

SUMMARY: These amendments designate a temporary restricted area identified as R-2309 in the vicinity of Bill Williams River Valley, Ariz., to contain high explosive detonations. These amendments provide for the safe and efficient use of the navigable airspace by prohibiting unauthorized flight operations of nonparticipating aircraft within the designated areas during the designated period.

EFFECTIVE DATE: July 13, 1978. Period of designation is August 27, 1978, through September 2, 1978.

FOR FURTHER INFORMATION CONTACT:

Mr. Richard Huff, Airspace Regulations Branch (AAT-230), Airspace and Air Traffic Rules Division, Air Traffic Service, Federal Aviation Administration, 800 Independence Avenue SW., Washington, D.C. 20591; telephone: 202-426-3715.

SUPPLEMENTARY INFORMATION:

HISTORY

On April 20, 1978, the FAA proposed to amend Parts 71 and 73 of the Federal Aviation Regulations (14 CFR Parts 71 and 73) to designate a temporary restricted area identified as R-2309 in the vicinity of Bill Williams River Valley, Ariz., to contain high explosive detonations and to include this restricted area in the continental control area for the duration of its time of designation (43 FR 16741). Interested persons were invited to participate in the rule making proceeding by submitting written comments on the proposal to the FAA. We received two responses to the NPRM in which the commenters posed no objections to the proposal. Sections 71.151 and 73.23 were republished in the *FEDERAL REGISTER* on January 3, 1978, (43 FR 344 and 664).

THE RULE

These amendments to Parts 71 and 73 of the Federal Aviation Regulations designate a temporary restricted area in the vicinity of Bill Williams River Valley, Ariz., to protect nonparticipat-

RULES AND REGULATIONS

ing aircraft from a large scale airblast associated with a high explosive field test program called Misers Bluff which involves the detonation of high explosives. In addition, the airspace at and above 14,500 feet MSL during the designated period (continuously from 0001 August 27, 1978, through 2400 hours, local time September 2, 1978) is included in the continental control area. These amendments adopt the airspace actions proposed in the NPRM (43 FR 16741). In accordance with established FAA policies, the using agency has provided the FAA with a statement that the requirements of the National Environmental Policy Act have been met.

DRAFTING INFORMATION

The principal authors of this document are Mr. Richard Huff, Air Traffic Service, and Mr. Richard W. Danforth, Office of the Chief Counsel.

ADOPTION OF THE AMENDMENT

Accordingly, pursuant to the authority delegated to me by the Administrator, Subpart D of Part 71 and Subpart B of Part 73 of the Federal Aviation Regulations (14 CFR Parts 71 and 73) as republished (43 FR 344 and 664) are amended, effective 0901 G.m.t., July 13, 1978, as follows:

In § 71.151, the following temporary restricted area is added for the duration of its time of designation from 001 hours, August 27, 1978, through 2400 hours, local time, September 2, 1978:

R-2309 MISERS BLUFF, ARIZ.

In § 73.23, the following temporary restricted area is added:

R-2309 MISERS BLUFF, ARIZ.

Boundaries. A circular area with a 10-nautical mile radius centered at lat. 34°15.5' N., long. 113°52.5' W.

Designated altitudes. Within a 3,000-foot radius centered at lat. 34°15.5' N., long. 113°52.5' W., surface to FL 320; within the circular area that lies between the 3,000-foot radius and the 10-nautical mile radius centered at lat. 34°15.5' N., long. 113°52.5' W., 100 feet above the surface to FL 320.

Time of designation. Continuous, 0001 August 27 through 2400 hours, local time, September 2, 1978.

Controlling agency. Federal Aviation Administration, Albuquerque ARTCC.

Using agency. Defense Nuclear Agency Field Command, Kirtland Air Force Base, N. Mex.

(Secs. 307(a), 313(a), Federal Aviation Act of 1958 (49 U.S.C. 1348(a) and 1354(a)); sec. 6(c), Department of Transportation Act (49 U.S.C. 1655(c)); and 14 CFR 11.69.)

NOTE.—The FAA has determined that this document does not contain a major proposal requiring preparation of an Economic Impact Statement under Executive Order 11821, as amended by Executive Order 11949, and OMB Circular A-107.

Issued in Washington, D.C., on May 23, 1978.

WILLIAM E. BROADWATER,
Chief, Airspace and Air
Traffic Rules Division.

[FR Doc. 78-14896 Filed 5-26-78; 8:45 am]

[6355-01]

Title 16—Commercial Practices

CHAPTER II—CONSUMER PRODUCT SAFETY COMMISSION

SUBCHAPTER C—FEDERAL HAZARDOUS SUBSTANCES ACT REGULATIONS

PART 1500—HAZARDOUS SUBSTANCES AND ARTICLES; ADMINISTRATION AND ENFORCEMENT REGULATIONS

Self-Pressurized Household Substances Containing Vinyl Chloride Monomer; Classification as Banned Hazardous Substance

AGENCY: Consumer Product Safety Commission.

ACTION: Confirmation of final order.

SUMMARY: The Commission announces that no objections have been filed within the statutory period to its final order of March 24, 1978 classifying any household substance in a self-pressurized container containing vinyl chloride monomer, manufactured or imported on or after October 7, 1974, as a "banned hazardous substance." In this document the Commission, therefore, confirms the final order.

DATES: The effective date of the rule declaring any household substance in a self-pressurized container containing vinyl chloride monomer to be a banned hazardous substance is June 22, 1978. The rule is applicable to products which have been manufactured or imported on or after October 7, 1974.

FOR FURTHER INFORMATION CONTACT:

Charles Jacobson, Consumer Product Safety Commission, Directorate for Compliance and Enforcement, Division of Regulatory Management, Washington, D.C. 20207, 301-492-6400.

SUPPLEMENTARY INFORMATION: On March 24, 1978 the Commission published in the *FEDERAL REGISTER*, 43 FR 12308, a final regulation pursuant to section 2(q)(1)(B) of the Federal Hazardous Substances Act (FHSA), 15 U.S.C. 1261(q)(1)(B), declaring any

¹Editorial note: The final regulation revised 16 CFR 1500.17(a)(10).

self-pressurized products intended or suitable for household use, manufactured or imported on or after October 7, 1974, that contain vinyl chloride monomer (VCM) as an ingredient or in the propellant to be "banned hazardous substances." The final regulation was a reissuance of an earlier fully retroactive ban (39 FR 30112) that had been set aside for failure to hold a hearing on objections to the retroactive effect of the regulation. (For a complete background discussion on the original ban, see the preamble to the March 24, 1978 notice.)

In the March 24, 1978 document the Commission affirmed its determination made in the original ban that self-pressurized household products containing vinyl chloride monomer are toxic hazardous substances within the meaning of the FHSA because of vinyl chloride monomer, which, when inhaled, has the capacity to produce substantial illness, specifically cancer. Because no safe level of human exposure to vinyl chloride monomer has been established, the Commission further affirmed its earlier finding that adequate cautionary labeling could not be written under the FHSA for self-pressurized household products containing VCM and concluded that the degree and nature of the hazard presented by the use of these products is such that the public health and safety can be adequately served only by keeping the products out of interstate commerce. In taking the banning action, the Commission noted that ample scientific evidence in the form of long-term animal bioassays and human epidemiological studies is available to demonstrate the carcinogenicity of vinyl chloride monomer by inhalation and to demonstrate that human exposure to the substance can result in angiosarcoma of the liver, a rare form of liver cancer.

The March 24, 1978 banning regulation also provided, as is required for the issuance of regulations pursuant to section 2(q)(1)(B) of the FHSA, that the procedures for rulemaking under section 701(e) of the Federal Food, Drug and Cosmetic Act would govern and that adversely affected persons could file objections and requests for a public hearing within 30 days of the publication of the Commission's final order.

The last day for the filing of objections with the Commission was April 24, 1978. Since no objections have been filed within the statutory period, the Commission in this document confirms its final order of March 24, 1978, declaring as banned hazardous substances any self-pressurized household products containing vinyl chloride monomer as an ingredient or in the propellant, manufactured or imported on or after October 7, 1974.

(Secs. 2(f)(1), (A), (B), (g), (q)(1)(B), 3(a), 74 Stat. 372, 374, as amended 80 Stat. 1304-05,

83 Stat. 187-189, 90 Stat. 503 (15 U.S.C. 1261, 1262); sec. 701 (e), (f), (g), 52 Stat. 1055-56, as amended 70 Stat. 919, 72 Stat. 948 (21 U.S.C. 371 (e), (f), (g)); sec. 30(a), 86 Stat. 1231 (15 U.S.C. 2079(a)).

Dated: May 23, 1978.

SADYE F. DUNN,
Acting Secretary, Consumer
Product Safety Commission.

[FR Doc. 78-14883 Filed 5-26-78; 8:45 am]

[4810-22]

Title 19—Customs Duties

CHAPTER 1—UNITED STATES CUSTOMS SERVICE, DEPARTMENT OF THE TREASURY

[T.D. 78-150]

PART 153—ANTIDUMPING

Carbon Steel Plate From Japan

AGENCY: U.S. Treasury Department.

ACTION: Finding of dumping; final rule.

SUMMARY: This notice is to inform the public that separate investigations conducted under the Antidumping Act, 1921, as amended, by the U.S. Treasury Department and the International Trade Commission, respectively, have resulted in determinations that carbon steel plate from Japan is being sold at less than fair value and that those sales are injuring an industry in the United States. On this basis, a finding of dumping is being issued and, generally, all unappraised entries of this merchandise will be liable for the possible assessment of special dumping duties.

EFFECTIVE DATE: May 30, 1978.

FOR FURTHER INFORMATION CONTACT:

Stephen Nyschot, U.S. Customs Service, Office of Operations, Duty Assessment Division, Technical Branch, 1301 Constitution Avenue NW., Washington, D.C. 20229 202-566-5492.

SUPPLEMENTARY INFORMATION: Section 201(a) of the Antidumping Act, 1921, as amended (19 U.S.C. 160(a)), gives the Secretary of the Treasury responsibility for determining whether imported merchandise is being sold at less than fair value. Pursuant to this authority the Secretary of the Treasury has determined that carbon steel plate from Japan is being sold at less than fair value within the meaning of section 201(a) of the Antidumping Act, 1921, as amended (19 U.S.C. 160(a)). (Published in the FEDERAL REGISTER of January 13, 1978 (43 FR 2032).) An "Amended Determination of Sales at Less Than Fair Value" was published in the FEDERAL REGISTER of March 27, 1978 (43 FR 12780).

Section 201(a) of the Antidumping Act, 1921, as amended (19 U.S.C. 160(a)), gives the United States International Trade Commission responsibility for determining whether by reason of such sales at less than fair value a domestic industry is being or is likely to be injured. The United States International Trade Commission has determined, and on April 18, 1978, it notified the Secretary of the Treasury that a domestic industry is being injured by reason of less than fair value imports of carbon steel plate from Japan. (Published in the FEDERAL REGISTER of April 24, 1978 (43 FR 17410)).

On behalf of the Secretary of the Treasury, I hereby make public these determinations, which constitute a finding of dumping with respect to carbon steel plate from Japan.

For purposes of this notice, the term "carbon steel plate" means hot-rolled carbon steel plate, 0.1875 (3/16) inches or more in thickness, over 8 inches in width, not in coils, not pickled, not coated or plated with metal, not clad, and not cut, pressed, or stamped to non-rectangular shape.

Section 153.46 of the Customs Regulations (19 CFR 153.46) is amended by adding the following to the list of findings of dumping currently in effect:

§ 153.46 List of current findings.

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Merchandise, country and T.D.

Carbon steel plate, Japan, 78-150.

(Secs. 201, 407, 42 Stat. 11, as amended, 18 (19 U.S.C. 160, 173).)

ROBERT H. MUNDHEIM,
General Counsel.

MAY 23, 1978.

[FR Doc. 78-15014 Filed 5-26-78; 8:45 am]

[4110-03]

Title 21—Food and Drugs

CHAPTER 1—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

SUBCHAPTER B—FOOD FOR HUMAN CONSUMPTION

[Docket No. 77N-0177]

SODIUM THIOSULFATE; AFFIRMATION OF GRAS STATUS AS A DIRECT AND AN INDIRECT HUMAN FOOD INGREDIENT

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: This rule affirms that sodium thiosulfate is generally recog-