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Effect of Exposure Route on Potency of Carcinogens

WILLIAM E. PEPELKO

Human Health Assessment Group, Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, 401 M Street, SW, Washington, DC 20460

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To compare the effectiveness of different exposure routes for the induction of cancer in experimental animals, the estimated dose associated with a 25% additional risk of cancer (RRD_{25}) was calculated using a group of carcinogenic agents for which both inhalation and oral ingestion cancer bioassays were available. Comparisons were made of 14 agents in rats and 9 in mice. Seven of the nine compared in mice were also compared in rats. Among rats, 8 of 14 agents were more effective via the oral route, while 7 of 9 were more effective via the oral route in mice. The variation in RRD_{25} values with route, however, was less than 10-fold for all the agents tested in mice and for 11 of 14 tested in rats. An overall difference in potency with route could not be detected statistically. In rats, differences in potency greater than 10-fold were found for asbestos, vinyl chloride, and hydrazine. In the case of asbestos, the agent was in the form of relatively insoluble particulate matter. The greater potency via inhalation is likely due to longer residence time of the particles in the deep lung than in the gut, allowing for a greater degree of particle dissolution with an accompanying increase in bioavailability. Vinyl chloride was generally tested by inhalation at doses high enough to saturate activation pathways, resulting in underestimates of low-dose potency. Many of the smaller potency differences with route, as well as those for hydrazine, were considered likely to be the result of variability in the design and/or quality of studies. It was concluded that, if the design and conduct of the experiments were adequate, if agents in the form of relatively insoluble particulate matter are eliminated, and if corrections are made to account for incomplete activation, then large errors during route extrapolation are unlikely to occur. © 1991 Academic Press, Inc.

INTRODUCTION

It is sometimes necessary to assess carcinogenic risk quantitatively using data for which the exposure route is different than the normal route of human exposure. This occurs most frequently with experimental animal studies that use the oral route, while the primary route of human exposure for the agent in question is inhalation. While extrapolation of cancer risk from the oral to the inhalation route has been carried out quite often, a systematic comparison of route-related potency along with an evaluation of the factors responsible for route-related differences in potency has not been performed.

The assumption most often made during route extrapolation is that carcinogenic potency as a function of applied dose is equivalent across both dose routes, i.e., that

the dose received from inhalation exposure expressed in terms of mg/kg body wt per day is equivalent to the same dose orally. This approach, however, ignores important pharmacokinetic and toxicokinetic considerations that may be responsible for differences in both carcinogenic and noncarcinogenic potency (Pepelko and Withey, 1985). Some of these are absorption efficiency, first-pass effects, portal-of-entry effects, and effect of route on degree of blood level fluctuation.

It is often possible to adjust for some of these uncertainties. Data regarding absorption efficiency are quite often available and can be taken into account quite simply. Information regarding first-pass effects (the degree of inactivation during first pass through the liver) can also be used to adjust the estimated target organ dose, assuming that the liver is not the primary target organ.

Other factors, however, are more difficult to adjust for. One example is a potential difference in target organ sensitivity when cancer occurs at a portal of entry. Another involves chemicals that are easily absorbed but have limited solubility in the blood or short active half-lives. In such cases the areas under the blood time-concentration curves are likely to be the same for equivalent doses administered by the oral or inhalation route (Trouwborst, 1982), but the shapes of these curves can be considerably different. During inhalation exposure, blood concentrations tend to reach an asymptote and remain stable with continuing exposure. With bolus dosing, common during oral exposure, blood levels can fluctuate greatly (Pepelko and Withey, 1985). This can result in different degrees of activation, varying toxic effects at the target organ, etc., all of which can affect carcinogenic potency.

The present study compares the carcinogenic potency of a variety of chemicals for which adequate long-term bioassays by both the inhalation and oral route of exposure are available, identifies factors responsible for large differences in potency with route, and attempts to adjust for them should they occur.

METHODS

The cancer potency data base of Gold *et al.* (1984) was surveyed to identify chemicals having long-term cancer bioassay data for both the oral and inhalation routes. The literature was searched to find potentially useful studies published since 1984. Certain unpublished studies listed in EPA documents were also used (Tables 1 and 2). Adequate oral and inhalation data were found for 14 chemicals tested in rats and for 9 chemicals tested in mice. In some of the oral studies the animals were dosed via gavage. Since we were unable to detect consistent differences in potency for chemicals tested by gavage or by administration in the food or water, they were not differentiated. All except asbestos are organic compounds. Unfortunately, no adequate companions were available for any of the metals or other agents in the form of relatively insoluble particulate matter. While positive inhalation data were available for some metals such as cadmium (Takenaka *et al.*, 1983) and beryllium (Schepers, 1961), oral studies were either of marginal significance or negative. Seven of the chemicals were adequately tested by both routes in mice and rats.

For each data set, the applied dose was expressed in terms of milligrams administered per day. Unless body weights were listed, mice were assumed to have a body weight of 0.03 kg and rats, 0.35 kg. Respiratory volumes over a 24-hr period were estimated using the following allometric equations as described by Anderson *et al.* (1983) and

inhalation data reported by Guyton (1950): 0.105 (body wt/0.113 kg)^{0.67} for rats, and 0.0345 (body wt/0.025 kg)^{0.67} for mice. After using body weight and respiratory volume to convert the exposure concentration to units of mg/day, the daily dose was adjusted to reflect the equivalent daily dose administered over a lifetime. For less-than-lifetime rodent studies, the daily dose was multiplied by the fraction of lifetime exposed. No adjustment was made for potential differences in absorption, since it was desired to initially test all the agents without making any corrections.

The adjusted daily applied doses and reported tumor incidences for each data set were used as inputs for the Global 86 multistage model computer program. The program was requested to provide both the maximum likelihood estimate (MLE) of dose and the 95% lower confidence limit on the dose associated with an additional risk of 0.25. The risk reference dose (RRD₂₅) is the MLE of the dose required to increase the probability of cancer to 25% + probability at dose zero. The use of additional risk in this study should not substantially affect the comparison of carcinogenic potency by dose route because very few of the data sets used reflected high background response rates. For those data sets having unusually high background rates, or decreasing rates of response at high concentration, due to acute toxicity or saturation of activating biochemical pathways, an additional risk of 0.25 did not yield a numerically stable estimate of RRD₂₅. The criterion for numerical instability was an observed percentage of cancer at the highest dose level less than 90% of the highest percentage observed at any dose. In these cases, Global 86 provided a warning and the RRD₂₅ value was excluded from further analysis. This occurred with tetrachloroethylene (in rats) and cadmium. An RRD₂₅ was calculated for each target organ showing a statistically significant increase in tumor incidence, as well as for total tumor incidence.

The approach described above generated a range of MLE and lower limit RRD₂₅ values for each of the two dose routes. To facilitate a comparison of carcinogenic potency by dose route, the geometric mean RRD₂₅ for each range of RRDs was computed by dose route and species using tumor incidences at all sites where a significant increase was detected.

If high dose levels are used for chemicals requiring metabolic activation, saturation of the activation pathway may occur. The tumor response then tends to reach a plateau and the RRD₂₅ value may be driven to an artificially high level. To attempt to account for this possibility, an MLE and lower bound RRD representing a 1% additional risk (designated as RRD₀₁) were also calculated for each data set.

RESULTS

The chemicals compared and the number of data sets examined for each species along with references are listed in Tables 1 and 2. The geometric mean RRD₂₅ values for the 14 agents having adequate cancer response data by both the oral and the inhalation routes in rats are summarized in Table 3. Nine comparisons for mice are listed in Table 4.

Except for vinyl chloride, asbestos, and hydrazine, the geometric mean RRD₂₅ values determined from oral bioassays are within an order of magnitude of the ones obtained from inhalation studies in rats. Two other compounds, tetrachloroethylene and cadmium, administered to rats by both dose routes could not be analyzed. In the case of cadmium, oral bioassays led to tumor responses that were

TABLE I
SUMMARY OF INFORMATION EXAMINED FOR EACH AGENT IN RATS

Agent	Oral		Inhalation	
	Number of data sets	Reference	Number of data sets	Reference
Acrylonitrile	28	Quast <i>et al.</i> , 1980b; Bio/dynamics Inc., 1980a-c, Behles <i>et al.</i> , 1980	12	Quast <i>et al.</i> , 1980a, Maltoni <i>et al.</i> , 1977
Asbestos (chrysotile)	1	Donham <i>et al.</i> , 1979	4	Reeves <i>et al.</i> , 1974, Wagner <i>et al.</i> , 1974, Davis <i>et al.</i> , 1978
- Benzene	7	Maltoni <i>et al.</i> , 1983	5	Maltoni <i>et al.</i> , 1983
- Cadmium compounds	1	Loser, 1980	2	Takenaka <i>et al.</i> , 1983
- Dibromochloropropane	12	NCI, 1977a; Hazleton, 1977	7	NTP, 1982c
- 1,2-Dibromoethane	4	NCI, 1978a	39	Wong <i>et al.</i> , 1982, NTP 1982a
- 1,2-Dichloroethane	6	NCI, 1978b	1	Maltoni <i>et al.</i> , 1980
- Dichloromethane	8	Serota <i>et al.</i> , 1986a; National Coffee Assn., 1982a	20	Dow Chemical Co., 1980, NTP, 1985; Kirschman <i>et al.</i> , 1986, Burek <i>et al.</i> , 1984
- Epichlorohydrin	7	Konishi <i>et al.</i> , 1980; van Esch, 1982	3	Laskin <i>et al.</i> , 1980
Ethylene oxide	4	Dunkelberg, 1982	23	Snelling <i>et al.</i> , 1981, Lynch and Moorman, 1982
Hydrazine	3	Severi and Biancifiori, 1968	4	MacEwen and Vernot, 1980
Propylene oxide	1	Dunkelberg, 1982	2	Reizel and Kuper, 1983
- Tetrachloroethylene	3	NCI, 1977b	29	Rampy <i>et al.</i> , 1978, NTP, 1986a
- Trichloroethylene	6	NTP, 1986b, 1987	4	Henschler <i>et al.</i> , 1980, Fukada <i>et al.</i> , 1983, Maltoni <i>et al.</i> , 1986
- Vinyl chloride	10	Feron <i>et al.</i> , 1981	18	Drew <i>et al.</i> , 1983; Hong <i>et al.</i> , 1981; Lee <i>et al.</i> , 1978; Maltoni, 1977; Maltoni and Lefemine, 1975; Maltoni <i>et al.</i> , 1981; Viola <i>et al.</i> , 1971
- Vinylidene chloride	16	NTP, 1982b	7	Maltoni <i>et al.</i> , 1985, Lee <i>et al.</i> , 1978, Quast <i>et al.</i> , 1986

too limited to yield a stable RRD_{25} estimate. At least two other metals, nickel and beryllium, yielded positive results via the inhalation route of exposure but not by ingestion (U.S. EPA, 1986, 1987). For tetrachloroethylene, the only available oral bioassay in rats failed to yield stable potency estimates because of excessive mortality.

TABLE 2
SUMMARY OF INFORMATION EXAMINED FOR EACH AGENT IN MICE

Agent	Oral		Inhalation	
	Number of data sets	Reference	Number of data sets	Reference
Dibromochloropropane	2	NCI, 1977a	8	NTP, 1982c
1,2-Dibromoethane	2	NCI, 1978a	17	NTP, 1982a; Stinson <i>et al.</i> , 1981
1,2-Dichloroethane	15	NCI, 1978b	1	Maltoni <i>et al.</i> , 1980
Dichloromethane	4	Nat. Coffee Assn., 1982b; Kirschman <i>et al.</i> , 1986; Serota <i>et al.</i> , 1986b	20	NTP, 1985
1,1-Dimethylhydrazine	7	Toth, 1973	8	Haun <i>et al.</i> , 1984
Hydrazine	12	Bianchini, 1970; Toth, 1969, 1972; Severi and Bianchini, 1966	1	MacEwen and Vernot, 1980
Tetrachloroethylene	2	NCI, 1977b	18	NTP, 1986a
Trichloroethylene	8	Herren-Freund <i>et al.</i> , 1987; Van Duuren <i>et al.</i> , 1979; NTP, 1986b; NCI, 1976	14	Henschler <i>et al.</i> , 1980; Bell <i>et al.</i> , 1978; Fukada <i>et al.</i> , 1983; Maltoni <i>et al.</i> , 1986
Vinylidene chloride	12	NTP, 1982c	11	Maltoni <i>et al.</i> , 1985; Lee <i>et al.</i> , 1978

The RRD_{25} values obtained for each route in mice are generally in closer agreement than those for rats. The only oral/inhalation RRD_{25} ratio approaching an order of magnitude was that for dibromoethane. The other ratios varied only from 0.6 to 2. Although oral/inhalation RRD_{25} ratios were less than one in the majority of comparisons, the small route-related differences in most cases and the variability in the data do not allow any generalizations regarding the likelihood that one route is more effective in mice.

Non-portal-of-entry, site-specific RRD_{25} comparisons were available for several of the agents evaluated. These are shown in Table 5. Differences in site-specific RRD_{25} values derived from oral versus inhalation studies paralleled the differences in mean RRD_{25} values for all tumor sites combined with some exceptions. Somewhat greater differences were seen for mammary gland tumors in rats exposed to acrylonitrile, while in mice exposed to vinylidene chloride, the inhalation route was slightly more effective for induction of mammary tumors, the opposite of that for all tumors combined. The relative potency for kidney and liver tumor induction differed less with route in rats exposed to vinyl chloride, but the oral route was still apparently much more potent for both sites. The apparent route-related difference in sensitivity to mammary tumor induction by acrylonitrile was probably due to large reported differences in background tumor incidence among studies. Overall, restricting the comparisons by tumor site did not substantially alter the observed relationship between potency by the oral and the inhalation routes.

Several of these agents are site-of-contact carcinogens (i.e., they induce stomach tumors by the oral route and nasal cavity or lung tumors by the inhalation route).

TABLE 3
GEOMETRIC MEAN RISK REFERENCE DOSES FOR SUBSTANCES ADMINISTERED TO RATS*

Agent	RRD ₂₅ (mg/day)			RRD ₁₀ (mg/day)		
	Oral	Inhalation	Oral/inhalation	Oral	Inhalation	Oral/inhalation
Acrylonitrile	5.3	8.5	0.6	0.4	0.73	0.5
Asbestos	647	5.9	109	64	0.21	305
Benzene	1008	389	2.6	87	14	4.2
Dibromochloropropane	1.7	0.8	2.2	0.12	0.065	1.9
1,2-Dibromoethane	2.2	14	0.2	0.08	0.56	0.1
1,2-Dichloroethane	20	67	0.3	1.4	4.4	0.3
Dichloromethane	374	1416	0.3	24	109	0.2
Epichlorohydrin	5.2	3.4	1.5	0.14	0.12	1.2
Ethylene oxide	5.6	6.4	0.9	0.75	0.92	0.8
Hydrazine	2.4	0.1	17	0.083	0.017	4.9
Propylene oxide	4.8	34	0.1	0.73	1.2	0.6
Trichloroethylene	1206	200	6.3	110	21	5.2
Vinyl chloride	5.2	219	0.02	0.23	8.9	0.03
Vinylidene chloride	3.3	11	0.3	0.32	2.1	0.2

* Geometric mean of range in RRDs across all tumor sites.

These include dibromochloropropane in rats and mice and dibromoethane and epichlorohydrin in rats. Ethylene oxide is a contact-site carcinogen by the oral route but is widely distributed in the tissues following inhalation exposure and induces leukemia as well as brain tumors when exposure occurs by this route. Despite the dissimilarities in site of action following exposure by the two routes, all of these substances showed similar carcinogenic potencies for either route of administration. Vinyl chloride was the only agent evaluated that induced tumors at the same portal-of-entry site, the lung, by both routes of exposure. Interestingly, the oral route was more potent, although the difference was less than for all tissues combined.

The effects of route on potency were examined statistically using a regression technique that considers that RRD₂₅ values for both dose routes are subject to statistical error (i.e., both are independent observations) (Kendall and Stuart, 1979). For rats, the regression describing the relationship is

$$\ln(\text{RRD}_{\text{inh}}) = 1.14(\ln \text{RRD}_{\text{oral}}) - 0.302.$$

The 95% confidence interval on slope is the range 0.33 to 3.37. The variability of the slope term is influenced by the large oral/inhalation differences obtained for vinyl chloride and asbestos. Omitting the results for these two substances changes the relationship to

$$\ln(\text{RRD}_{\text{inh}}) = 1.28(\ln \text{RRD}_{\text{oral}}) - 0.866.$$

The 95% confidence interval on slope then decreased to a range of 0.35 to 1.79. Regardless of whether the data for vinyl chloride and asbestos are included, both analyses show that a slope of 1 cannot be ruled out; that is, there is no statistical basis for discarding the hypothesis that carcinogenic potency, expressed as a function of applied dose, is the same regardless of whether the dose is administered by the oral or inhalation route.

TABLE 4
GEOMETRIC MEAN RISK REFERENCE DOSES FOR SUBSTANCES ADMINISTERED TO MICE*

Agent	RRD ₂₅ (mg/day)			RRD ₀₁ (mg/day)		
	Oral	Inhalation	Oral/inhalation	Oral	Inhalation	Oral/inhalation
Dibromochloropropane	0.35	0.26	1.3	0.016	0.015	1.1
1,2-Dibromoethane	0.19	1.5	0.1	0.007	0.17	0.04
1,2-Dichloroethane	4.6	7.8	0.6	0.69	3.6	0.2
Dichloromethane	49	52	0.9	1.5	6.2	0.2
1,1-Dimethylhydrazine	0.36	0.17	2.0	0.018	0.009	2.1
Hydrazine	0.04	0.06	0.7	0.001	0.002	0.6
Tetrachloroethylene	4.4	4.8	0.9	0.23	0.69	0.3
Trichloroethylene	21	23	0.9	0.84	1.9	0.5
Vinylidene chloride	1.0	1.6	0.6	0.08	0.09	0.9

* Geometric mean of range of RRDs across all tumor sites.

For mice, the regression analysis resulted in the relationship

$$\ln(\text{RRD}_{\text{inh}}) = 1.03 \ln(\text{RRD}_{\text{oral}}) + 0.25.$$

The 95% confidence interval on slope is 0.16 to 4.81. Thus, the relationship between carcinogenic potency of these substances in mice treated orally compared with those treated by inhalation is very similar to the relationship derived from rat studies. As was the case for rat studies, the RRD₂₅ values obtained from the mouse studies cannot be used to rule out the hypothesis that exposure route does not influence carcinogenic potency.

In addition to RRD₂₅ values, all data sets for each chemical were used with Global 86 to compute the MLE and lower-bound RRD representing a 1% additional risk (designated as RRD₀₁). This risk level is below the observable range in bioassays. This calculation was made because some chemicals may be activated through a rate-limiting mechanism causing the cancer response to level out at higher concentrations. This could drive the RRD value to an artificially high level, because of the apparently decreased potency at the high doses. Since the RRD₀₁ is likely to be below metabolically saturating levels, a more accurate estimate of potency may be obtained for such agents.

Examination of Tables 2 and 3 shows that, in the majority of cases, the ratio of oral to inhalation RRD values was altered only modestly by calculating a 1% additional risk as compared with 25%. The difference was equal or less than twofold for 15 of the 23 comparisons in mice and rats and equal or less than threefold for 20 of the 23 comparisons. The maximum change ranged from about four- to sixfold for hydrazine and propylene oxide in rats and dichloromethane in mice. Unexpectedly, vinyl chloride, a chemical known to require activation and administered in the inhalation studies at saturating doses, showed little change in the oral/inhalation ratios at 1% compared with 25%.

As can be seen in Tables 3 and 4, oral and inhalation RRD values for both mice and rats are listed for seven chemicals, dibromochloropropane, 1,2-dibromoethane, 1,2-dichloroethane, dichloromethane, hydrazine, trichloroethylene, and vinylidene chloride. The geometric mean of oral RRD₂₅ values for these seven chemicals equaled

TABLE 5
COMPARISON OF RRD₂₅ AT IDENTICAL NONPORTAL OF ENTRY SITES*

Agent	Tumor site	Oral	Inhalation	Oral/inhalation
Rats				
Acrylonitrile	Zymhal gland	10	26	0.4
	Mammary gland	0.66	8.3	0.1
	Brain, spinal cord	3.3	9.5	0.4
Benzene	Zymhal gland	1008	283	3.6
1,2-Dichloromethane	Mammary gland	12	67	0.2
Dichloromethane	Liver	245	922	0.3
Trichloroethylene	Kidney	1096	262	4.2
Vinyl chloride	Liver	4.9	89	0.05
	Kidney	5.1	2334	0.002
Vinylidene chloride	Pancreas	2.8	25	0.1
	Thyroid	3.9	30	0.1
Mice				
1,2-Dichloroethane	Mammary gland	2.8	7.8	0.4
Dichloromethane	Liver	37	64	0.6
Tetrachloroethylene	Liver	4.4	4.5	1.0
Trichloroethylene	Liver	21	32	0.7
Vinylidene chloride	Mammary gland	0.44	0.20	2.2

* Non-portal-of-entry sites, i.e., excluding the respiratory and gastrointestinal tracts.

16 for rats versus 1.4 for mice. The means for the inhalation values equaled 15.5 for rats versus 2.3 for mice. Thus, the mice are apparently more sensitive to this group of chemicals than rats. The reason for these results is uncertain. Since mice are smaller, with a greater metabolic rate, it could be predicted that they would respond to a lesser degree to the same dose per milligram body weight than rats. Possible explanations include greater sensitivity of the target organs in mice, more efficient activation for those chemicals requiring activation, and more efficient absorption. In several of the studies with mice, the liver was the primary target organ. Since mice respond to many chemicals by the induction of liver tumors, the liver may well be a sensitive target organ and thus be responsible for the low RRD values. In any case, for this set of chemicals, the use of mouse data will result in greater potency estimates for humans, extrapolating on a mg/kg body wt basis, than if rat data are used. If a body surface area correction is used, the differences in human potency estimates for mouse and rat data will become even greater.

DISCUSSION

There is probably no way to compare cancer potencies in a simple straightforward manner with a high degree of precision and accuracy. The 25% response rate was selected because it was expected to be in the observable range for most studies, thus not requiring extrapolation. Unfortunately this was not always true. Moreover, the dose-response curve does not always continue in a straight line to 100%, but may flatten out at much lower response levels due to saturation of activation pathways, or may even decrease at high dose levels due to acute toxicity. Global 86 produced a

warning when the data fit poorly and these data sets were eliminated. Nevertheless, some data sets produced at concentrations known to result in saturation of activation pathways were not eliminated by this warning. Thus it is important to have as much knowledge of metabolism and acute toxicity as possible when attempting potency comparisons.

This analysis of the relationship between carcinogenic potency and route of administration generally demonstrated that the carcinogenic potencies of most of the substances examined were not substantially influenced by dose route. While differences were somewhat greater in rats than mice, data were not available in mice for the two agents showing the greatest differences in rats.

Several factors may affect the carcinogenic potency of an agent with route. If the effects occur at a portal of entry, then the target organ will be different for the gastrointestinal and inhalation routes. Lacking further information, the potential differing sensitivities of these organs can result in an unquantifiable amount of uncertainty if route extrapolation is attempted. As mentioned previously, among those three or four agents inducing respiratory tract tumors via inhalation and stomach tumors orally, little difference in potency was seen.

Another important factor is absorption efficiency. Among the organic chemicals compared, vinyl chloride showed the largest route-related difference in RRD_{25} . Although the literature was not searched for information relating to absorption for most of the agents evaluated, based upon the lack of large differences in potency, it is unlikely that this is a major factor in many instances. In the case of vinyl chloride, there is some evidence that absorption efficiency via the oral route is about twice that by inhalation (Feron *et al.*, 1981; Krajewski *et al.*, 1980) and could thus account for some of the difference in potency for this chemical.

Many pollutants, however, are in the form of solid particulate matter. These include asbestos, manmade mineral fibers, combustion products, and various metal compounds. When inhaled, a portion is deposited in the alveolar regions where it can remain for relatively long periods, allowing for dissolution of relatively insoluble particles, and thus rendering them bioavailable. On the other hand, little or no solubilization may occur during the relatively rapid passage through the gastrointestinal tract. This was seen quite clearly in the case for asbestos. Similarly, a stable estimate of RRD_{25} could not be obtained for cadmium via the oral route because of the low response. Two other metals, beryllium and nickel, also induced cancer via the inhalation route, but not orally (U.S. EPA, 1986, 1987). Based upon these findings, route extrapolation for agents in the form of inhaled particulate matter does not appear to be feasible unless data regarding bioavailability by both routes are known.

Many organic chemicals require activation before induction of mutational changes leading to cancer. If the rate-limiting step occurs during activation rather than breakdown, then the carcinogenic response will not be expected to increase linearly with dose at high concentrations. The large oral/inhalation RRD differences for vinyl chloride are likely the result of this factor. While the doses used in the oral studies were well below those necessary to saturate activation pathways, many of the inhalation studies used much higher concentrations, some as high as 10,000 ppm or more.

To determine if metabolic saturation is a major factor in the large oral/inhalation RRD differences for vinyl chloride, the inhalation data set of Drew *et al.* (1983) was examined. These researchers exposed female Fischer 344 rats to 100 ppm vinyl chloride 6 hr/day for 24 months. Since the k_m , or concentration at half-saturation, was reported

to be 860 ppm for a 6-hr exposure (Gehring *et al.*, 1978), the percentage activation should be near 100%. The geometric mean RRD_{25} value for all tumor sites reported in this study was only 16.3 mg/day, less than one-tenth the value derived as the mean of all inhalation studies, and not much greater than the mean for the oral studies. If a further adjustment is made for an approximately twofold greater absorption efficiency by the oral route, the inhalation RRD_{25} value would be little different from the oral value of 5.2. Thus, at exposure levels below saturation of activation pathways, there does not appear to be a true route-related difference in carcinogenic potency for vinyl chloride.

Dibromo- and dichloroethane are two other chemicals requiring activation whose pharmacokinetics have been studied (U.S. EPA, 1985). While oral/inhalation RRD_{25} differences are much less than those for vinyl chloride, it is likely that if k_m values were known, adjusting for the degree of activation would result in even better agreement.

Hydrazine is the only other chemical with oral/inhalation $RRDs$ differing by more than 10-fold in rats. There is no apparent pharmacokinetic explanation for this difference, especially since route had little effect on potency in mice. Moreover, potency via the inhalation route differed to only a small degree in mice and rats. While a large number of oral studies were available for mice, only one was reported using rats (Severi and Biancifiori, 1968). In this study only one exposure level was used and the number of animals assayed was small, 13 to 18 per sex. The potential variability when only one such experiment is available may well have accounted for much of the apparent difference in potency with route in rats.

For the remaining organic compounds, the observed dose-route-related differences in carcinogenic potency are not substantial. In fact, the potency values derived from different studies involving the same substance and the same dose route generally varied to a greater extent than values for the same substance administered by different routes. As was likely the case for hydrazine, the small differences seen may often be the result of differences in study design or quality. The underlying data for one compound, 1,2-dichloroethane, were examined more closely to evaluate the likelihood of such an explanation. This compound was chosen because there appeared to be little variation in the potency estimates derived from studies involving the same route.

For 1,2-dichloroethane, there is a threefold difference in the mean potency values for oral and inhalation dose routes; the oral route is more potent. The potency value for the inhalation route derives from a single study in Sprague-Dawley rats (Maltoni *et al.*, 1980); in this study there was a high background rate of mammary tumors and a marginal tumorigenic response. Different strains of rats were used in oral bioassays of this compound (NCI, 1978b), and in these studies, the background rates were low and the tumor response was statistically significant. The difference in response may therefore be a reflection of both differences in background rates and responsiveness with strains. The smaller difference in RRD_{25} with route in mice also suggests the lack of a true route-related difference in potency.

It should be recognized, however, that route-related differences in carcinogenic potency are minimized if only agents testing positively by both routes are considered. An attempt was therefore made to estimate the prevalence of chemicals testing positive by only one route. Two sources of information were reviewed, the EPA's Integrated Risk Information System (IRIS) and the Office of Solid Waste and Emergency Response's reportable quantities documents. Both sources provided short reviews and

cancer assessments for a large variety of chemicals. For purposes of this review, chemicals that were shown to induce cancer following intratracheal instillation as well as inhalation were considered to be positive by the respiratory route.

Positive cancer responses by the oral or respiratory route, not including the ones used for calculation of RRDs, were reported for 120 agents. Unfortunately, adequate bioassay data by both routes were reported for only 13 of the 120. Of these, 10 were positive by both routes. These 10 were not used for RRD calculation because either the species differed, intratracheal instillation was used, or the data set was inadequate for quantitation. Another three, nickel subsulfide, cadmium, and beryllium, were positive by inhalation, but negative via the oral route. None of those adequately tested by both routes were positive by only the oral route.

Thus, including chemicals used for RRD calculation, 26 of 29 adequately tested were positive for cancer by both routes. The only definite exceptions were agents in the form of relatively insoluble particulate matter. Among poorly soluble aerosols, even those testing positively by both routes, such as asbestos and certain cadmium compounds, were more effective via inhalation. As mentioned previously, their greater effectiveness via the inhalation route is probably due to a longer residence time, allowing for greater solubilization. If poorly soluble particulate matter is excluded, then the likelihood of carrying out a route extrapolation on an agent having widely differing cancer potency with route will be decreased.

CONCLUSIONS

In the absence of cancer bioassay data for either the oral or inhalation route, it was found that extrapolation is less likely to result in large errors in potency estimates if (a) the agent is in vapor, liquid, or relatively soluble solid form; (b) the design and quality of the available studies are good; or (c) the doses used are not great enough to saturate either activation or deactivation pathways. It is also important to determine if (d) absorption efficiency differs greatly with route, (e) whether the agent acts systemically or at a portal of entry, and (f) if there are major first-pass effects. If the above factors can be adjusted for, then large differences in potency with route are much less likely to occur. It should be noted, however, that the findings are based upon a limited number of comparisons. Until cancer bioassays by both routes, along with pharmacokinetic studies, have been carried out on a much larger number of chemicals, considerable uncertainty will continue to exist when extrapolating potency from one route to another.

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