TOXICOLOGICAL SCIENCES **50,** 164–168 (1999)

Some Notes on the History of Haber's Law

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Received on February 2, 1999; accepted on April 1, 1999

A Brief History of Haber's Law

Haber's law or rule, as commonly understood in inhalation toxicology, states: $C \times T =$ constant, meaning that identical products of concentration of an agent in air (C) and duration of exposure (T), the CT product, will yield an identical biological response. The formula was originally developed by the German physical chemist Fritz Haber (1868–1934) to characterize the acute toxicity of chemicals used in gas warfare (for a brief history of the life of Fritz Haber, see Witschi, 1997). Eventually, this simple equation was used as scientific basis for the setting of exposure limits (see Atherley, 1985 and Henschler, 1984 for a critical discussion of the CT concept in standard setting). Animal experiments show that the rule does not always apply. When the effects of phosgene on pulmonary gas exchange were measured within a time interval of 5 min to 8 h, it was concluded that "there was no indication that concentration contributed more than exposure time to the magnitude of change in pulmonary performance over the range of CT values studied" (Rinehart and Hatch, 1964). In this experiment, the rule was valid. On the other hand, when the effects of subchronic phosgene exposure were examined, the unequivocal conclusion was reached that phosgene concentration rather than $C \times T$ product appeared to drive the toxic response (Kodavanti *et al*. 1997). In studies with another acutely toxic agent, ozone, similar observations were made: when protein retrieved from bronchoalveolar lavage fluid was measured as the toxicological endpoint, Haber's rule was valid (Gelzleichter *et al*. 1992; Highfill *et al*. 1992). When the identical exposure protocol was used, but a different endpoint was measured (cell renewal in the airways), the concentration of the inhalant or the dose rate at which ozone was delivered appeared to be the driving determinant of toxicity (Rajini *et al*. 1993). Experiments designed specifically to test the validity of the CT concept thus can either confirm it or contradict it, and often the conclusions that are drawn depend upon the toxicological endpoints that were measured. Nevertheless, it is generally agreed that the CT could not apply to an infinite time of exposure, or there would be no safe exposure limits for prolonged or repeated exposures. Concentration of an airborne agent, which eventually will determine the dose, is generally considered the most important determining factor in toxicity.

The importance of dose as a variable in toxicology has been recognized since Paracelsus. The importance of time is usually less well understood, but appears to be of equally fundamental significance, and some recent experiments shed indeed some new light on the CT concept (Rozman, 1999; Rozman *et al*. 1998). It is therefore appropriate to go back and take a closer look at the origins of Haber's law and at how it was interpreted by the scientists who developed the concept.

The Original Paper by Flury

The CT product was used in the development of war gases and, according to Haber (1924), served as a "simple and sufficiently practical gauge of toxicity" (Table 1). In a paper on poisoning by war gases, Flury extensively developed the formula and illustrated it by data from his own experiments (Flury, 1921). The original text is of sufficient interest that it deserves to be made available again to today's audience. The following is a translation of Flury's thoughts on the CT concept:

> *As was shown in many thorough investigations, the effects of different irritating gases can be quantitated and expressed with quite good accuracy. Not only are such measurements of fundamental significance in gas warfare, but they are also valuable from a general toxicological standpoint, since certain of the investigated agents, e.g., phosgene, are widely used in the chemical industry, whereas others, such as certain hydrocyanic acid derivatives and chlorpicrin, will probably be used in the future quite extensively to control pests that adversely affect plants. The literature provides reliable quantitative data only on the better known industrial poisons; the experiments conducted by K. Lehman and his students on the important group of industrial gases being the most thoroughly conducted.*
>
> *In order to evaluate the efficiency of a poison, it is customary to consider the following equation:*
>
> $$g/G = Z$$

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TABLE 1
The Original Haber Formula

Gas	$C \times T$
Phosgene	450
Methylchloroformate	500
Hydrocyanic acid*	1000
Chloracetone	3000
Xylylbromide	6000
Chlorine	7500

*The value of $C \times T$ for hydrogen cyanide depends upon its concentration. The value given refers to the concentration of 0.5% obtainable in the field. *The values are much higher with smaller concentrations* [emphasis added].

Footnote No. 3 in Haber's 1924 paper: "A simple and practical measure for toxicity can be obtained that suffices for all practical purposes. For each war gas, the amount *(C)* present in one cubic meter of air is expressed in milligrams and multiplied by the time *(T)* in minutes necessary for the experimental animal inhaling this air to obtain a lethal effect. The smaller this product, $C \times T$, the greater the toxicity of the war gas. A few values obtained during the war are given in the table. More detailed information can be found in the medical literature. The values were all obtained by using cats as experimental animals".

with g denoting the amount of poison taken up, G the body weight of the experimental animal, and Z the number where a certain effect, for example death, occurs.

As far as inhaled poisons are concerned, it is possible to define g as a product of three factors: the number of milligrams of the poison present in one cubic meter of inspired air (C), the number of minutes (T) during which air with the concentration C of the poison was inhaled, and finally A, expressed in cubic meters, the volume inhaled by the animal per minute:

$$g = C \times T \times A$$

When substituted into the previous formula:

$$C \times T\, A/G = Z$$

If one considers, in a first approximation, the quotient A/G, i.e., minute volume, in relation to body weight, as being independent of the individual animal within a given species and independent of the particular experimental conditions, it becomes possible to replace the quotient by a constant and to combine this together with Z into one. This provides "Haber's formula:"

$$C \times T = W$$

whereby W may be called the effects product (Wirkungsprodukt) or, in the special case where there is lethal poisoning, "lethality product" (Toedlichkeitsprodukt). It is the inherent merit of this approximation that it becomes possible to compare, with reasonable accuracy and considerable ease, the effects of rather different toxic inhalants. However, the formula has some limitations, inasmuch as the effect produced is only constant within certain concentration limits, but not within any range of arbitrarily selected concentrations [emphasis added]. *With agents of the type of phosgene, the range of concentrations spans approximately the range within which it is possible to conduct experiments [see Table 2 for some of Flury's data]. Experiments are limited on one side by the fact that, at high concentration time, t becomes too short. This is easily understandable if one considers what kind of imprecision is introduced whenever time t in the formula (i.e., 1 to 2 min) is no longer great compared to the time it takes for a single breath. On the other hand, it is impossible to work with such small concentrations whenever the limit of detection in the analytical procedures becomes the source of substantial errors.* However, the formula becomes a practical tool whenever it still applies to a t of a few minutes, and on the other hand, remains valid for such small concentrations that *C* represents a few milligrams per cubic meter. Within those limits, the effects product for phosgene and many other agents is quite good [emphasis added].

TABLE 2
Some of Flury's $C \times T$ Values for the Effects (Haber Product) of Phosgene on Cats

Concentration (mg/m^3)	Breathing time (min)	Product, $C \times T$	Results
5	60	300	Survives
10	15	150	Slightly sick
12.5	60	750	Death after 1 day
10	120	1200	Death after 1 day
20	25	500	Survives (sick)
25	60	1500	Death after 1 day
75	5	375	Survives
100	5	500	Death after 1 day
500	1	500	Survives
500	3	1500	Death
500	2	1000	Sick, death after 9 days

Note. Data from Flury (1921).

However, not all gases have constant effects product [emphasis added]. *Agents of the same type as hydrocyanic acid represent the most notable exception. If one considers the limits where death occurs, the $c \times t$ product tends to increase with decreasing values of c (see Table 3). Agents that are toxic only after their resorption, such as hydrocyanic acid and related compounds, are gradually better tolerated as the concentration at which they are inhaled becomes smaller. This can be formulated in its simplest way as follows, by introducing a constant detoxification factor, e:*

TABLE 3
Some of Flury's $C \times T$ Values for the Effects (Haber Product) of Hydrocyanic Acid on Cats

Concentration (mg/m^3)	Breathing time (min)	$C \times T$	Result
500	2	1000	Death
350	4	1400	Death
335	10	3350	Death
240	15	3600	Death
150	8	1200	Survives
150	15	2250	Survives
150	40	6000	Survives
150	70	10,500	Death
125	180	22,500	Survives (sick)
40	90	3600	Survives
40	120	4800	Death

Note. Data from Flury (1921).

$$(C - e)\,T = W$$

This assumption is usually sufficient to describe observations made, although it is certainly not accurate: theoretically, it is not satisfactory to assume that the formula for hydrocyanic acid and related agents is only valid at a concentration above a certain threshold value, whereas all smaller amounts should be detoxified within the body. However, the development of more refined formulas could only be justified if experimental data should become so reproducible as to allow a critical test of such a theory.

It is a definite advantage of Haber's effects product that its order of magnitude remains the same for different species. For practical purposes, it is not necessary to determine separate values for different mammalian species (cats, dogs, monkeys). The differences in the magnitude of W between the various species is dwarfed by the much greater differences in W between the various chemicals.

Flury thus makes several points not always fully considered by later advocates of Haber's law. Perhaps the most important one is that the effects product for hydrocyanic acid does not remain a constant, but increases with decreasing concentrations of the toxicant in the inspired air. Flury expanded this concept in a later series of experiments on the narcotic effects of several solvents (Flury and Wirth 1934). Here, he came to the conclusion that concentration is more important than time:

Both the table and the curves (exemplified by the effects of methylacetate) show clearly that the amounts needed to produce a certain stage of narcosis are not constant, but rather show a characteristic pattern of dependency upon their concentration in the inhaled air. The narcotic effects are comparatively less pronounced at lower concentrations than at higher ones; i.e., at lower concentrations the inhaled amounts needed to produce a given stage of narcosis are greater than those required at high concentrations, where less is needed. In our experiments with methyl acetate, about a tenfold difference was found. Similar findings were made with the other narcotic esters. The dependence of the effects product on concentrations may possibly be attributed to the fact that, at low concentrations, detoxification processes are more efficient than they are at high concentrations [emphasis added]. *In addition, other physico-chemical factors may play a role.*

These then are the thoughts Flury had on the general applicability of "Haber's rule". It has been stated that Haber's rule really should be named "Flury's rule," because Flury published the formula earlier and appeared to have experimental data (Atherley, 1985). However, in his paper, Flury (1921) explicitly refers to the "Haber'sche Regel." Who then was Flury, and how did he relate to Fritz Haber? In the following, a few facts on Flury's life and accomplishments are presented. The two recent and extensive biographies on Fritz Haber (Stoltzenberg, 1994; Szollosi-Janze, 1998), and a chapter from a "Festschrift" produced by the University of Wuerzburg, Germany, on occasion of its 400th anniversary (Henschler, 1982), served as sources.

Ferdinand Flury (1877–1947)

Between the first and second world wars, Ferdinand Flury was one of the most distinguished investigators and teachers in industrial toxicology. He obtained a Ph.D. in pharmacy in 1902 and, in 1905, a license as a food chemist. He got his M.D. in 1910. During his studies, he traveled widely and became fluent in seven languages. He also developed a career in the military, serving as pharmacist to an army corps. In 1915, he was appointed professor of pharmacology at the University of Wuerzburg.

Shortly thereafter, he was called to the Kaiser Wilhelm Institute for Physikalische and Elektrochemie, located in the Berlin suburb of Dahlem. There, Fritz Haber had assembled a large team, consisting eventually of more than 150 scientists and 1300 technical personnel. Their task was to develop the tools of gas warfare and, at the same time, to design countermeasures such as efficient gas masks. Flury was the leader of department E and, together with a staff of 10 scientists and 15 assistants, was responsible for studies on the toxicity of war gases, animal experiments, and industrial hygiene. He conducted experiments with rats, mice, guinea pigs, dogs, monkeys, and even horses. He studied the acute inhalation toxicity of numerous agents thought to be useful in gas warfare.

His work on mechanisms of toxicity of gases used in warfare led to the development of effective methods of treatment and countermeasures against gas toxicity. However, his department also was deeply involved in the development and testing of new chemical agents. The capacity of phosgene to produce delayed fatal pulmonary edema following exposure to small, not even noticeable concentrations was discovered. Another agent that was widely studied was hydrocyanic acid. During World War I and thereafter, there was a widespread need for pest control, particularly in granaries and flourmills. Whole buildings had to be fumigated. At an entomology congress in 1918, Flury described the use of hydrocyanic acid and the improved methods of its delivery and of measurement, which had been developed. Originally, paper bags filled with sodium or potassium cyanide were placed beside vats filled with dilute sulfuric acid. A technician then emptied the contents of the bags into the sulfuric acid while working his way towards the exit of the room. The procedure was obviously hazardous, and so better methods had to be developed. In such an improved process, hydrocyanic acid and a strong irritant, for example xylilbromide, were bound to an inert carrier (infusorian earth) and kept within tin cans. When the cans were opened and the material dispersed onto the floor of a room, both the cyanide and the irritant evaporated, the irritant serving as a warning sign for the presence of the lethal gas. The process was called the "Zyklon system." It was later commercialized and several companies were licensed to manufacture it. One product, called Zyklon B, eventually became infamous in world War II as the material used for mass exterminations in the death camps. For this purpose, the irritant that was usually added had been removed, on orders of the SS. After the war, the director of one company who had delivered Zyklon B to the SS was condemned to death.

In 1920, when Haber's institute had been reduced to practically one department, Flury moved to the University of Wurz-

burg and a most distinguished career in industrial hygiene and toxicology. He authored several classical textbooks, among them *Lehrbuch der Toxikologie* (together with Zangger) and *Toxicology and Hygiene of Industrial Solvents* (together with Lehmann). At times, more than 30 researchers worked in his institute, many of them coming from as far abroad as Japan and the United States. His main interest was in industrial toxicology, and the concept of a scientifically based setting of threshold limit values originated from his work. As he had done in Dahlem, he studied the toxicity of gases and vapors in dynamically operated (flow-through) inhalation chambers. Flury was highly respected by his colleagues and when, in 1932, the University of Wuerzburg celebrated its 350th anniversary, he was elected as rector for that particular year.

He was again called for his expertise on gas warfare in the years leading up to and during World War II. According to Henschler (1982), he warned against the use of gases whose deleterious actions he knew so well. Towards the end of the war, when there was a general breakdown of command structures, his influence seemed to have been instrumental in preventing the use of chemical weapons. In March 1945, the University of Wuerzburg and Flury's institute were destroyed by bombs. Flury was dismissed in 1945. According to Kehoe, who wrote an obituary upon learning of his death (1948), "At the end of the war, he being technically a brigadier general in the Wehrmacht, became automatically a prisoner of war and was able to return to Wuerzburg and the University only a few months before his death."

The *CT* Concept in Carcinogenesis

The original and most of the of the older and newer literature that deals with Haber's law clearly recognizes its potential limits and caveats, such as endpoints measured (toxicodynamics) and the role of metabolism (toxicokinetics) that need to be considered when applying the "law" in acute-exposure scenarios. But what about long-time exposures? Unfortunately, much less information is available. In 1948, Druckrey attempted to examine the *CT* concept in some of his carcinogenesis experiments (Druckrey and Kuepfmueller, 1948). He conducted a study with the potent hepatocarcinogen, dimethylaminoazobenzene ("butter yellow"). He treated rats with 0.5, 1.5, 5, or 15 mg/kg of the carcinogen per day, administered in the food, or with 50 or 150 mg/kg per day, administered by gavage. Endpoints examined were the development of hepatocellular carcinomas. Results are presented in Table 4. When the total dose was defined as a $C \times T$ product, there was a clear dose-response; the higher the $C \times T$ product, the shorter the latency period or time to tumors. However, the total dose necessary to produce tumors was given by the *CT* product: for daily doses of 3 mg or more; the total dose required to produce tumors was approximately 1000 mg for a 200-g rat. Induction of tumors did thus not depend on dose rate or concentration of carcinogen in the feed but on total dose. Druckrey concluded

TABLE 4
Druckrey's $C \times T$ Values for the Effects (Haber Product) of Dimethylaminoazobenzene on Rats

Doses (mg/kg/day)	Latency period (days)	Total dose (mg)	Mean life expectancy (days)
0	–	–	500
0.5	–	–	500
1.5	>800	>240	500
5	705	688	500
15	350	1050	500
50	95	950	86
100	52	1040	52
150	34	1020	32

Note. Data from Druckrey and Kuepfmueller (1948).

that "the duration of the latency period, i.e., the time of treatment necessary to produce the effect W (= Wirkung) is inversely proportional to the daily carcinogen dose c, i.e., $C \times T$ = constant or W approximates $C \times T$." The experiments show that (a) the latency period is a function of the daily dose; (b) to produce tumors, a certain total dose is necessary, regardless of how it is distributed between 35 and 365 days, latency period being inversely related to the daily dose; and (c) if experiments are extended over the lifespan of the animals, a smaller dose is necessary to produce an effect, indicating that, with increasing age, there is increasing disposition to develop tumors. According to Haber's concept, the effects-product for butter yellow would thus be approximately 1000 mg for a 200-g rat.

Druckrey then goes on to comment on the interpretation of his results:

> *Pharmacology knows a great many agents whose effects are determined by the (constant) concentration, C, of the poison and the time of exposure, T, or in general terms, by the integrated product of concentration and time. These are called 'CT poisons'. A necessary prerequisite for such a behavior is the binding of the agent at its target, or an irreversible effect resulting in a summation of its effects. As far as presently known CT poisons are concerned, this is only valid for a limited range of time and concentration; with regard to time, this range is hours or, at best, days. This limitation is due to the fact that during prolonged time periods there can occur a certain reversibility or repair processes; are small concentrations applied over prolonged time intervals, there will be higher CT values found than in shorter experiments with higher concentrations.*
>
> *Nevertheless, our data show a constant CT product, even if they lasted one year, and, when the duration of the experiment was doubled, involving the entire life span of the animals, the CT product became even smaller. The carcinogenic effect of butter yellow was thus, even at the smallest doses, irreversible from the beginning of the experiment during the entire life span of the animals, and is additive with further exposure without any modifications until, after a critical total dose has been exceed, the tumors develop.*

Outlook

To what extent then, in the *CT* concept, is there a fundamental principle in toxicology? As mentioned earlier, it is not

always possible to "prove" its validity in experimentation, and it is generally thought that concentration may be more important than time. However, it has been argued that time is an equally important factor in risk assessment and that dose alone will not suffice (Rozman, 1998). The *CT* concept appears to be a fundamental principle in toxicology that can be seen clearly under ideal conditions. One criterion appears to be the need for a toxicokinetic steady state. Such conditions could be accomplished by studying a compound with a highly lipophilic chemical of very long half-life after oral administration. In a recent paper, Rozman could show, indeed, that the oral toxicity of 1,2,3,4,6,7,8-heptachlorodibenzo-p-dioxin followed the *CT* concept (Rozman, 1999). This led him to postulate that the famous statement by Paracelsus, "The dose makes the poison" should be amended to "Dose and time make the poison." Future experimentation is needed to explore this concept more thoroughly.

ACKNOWLEDGMENTS

This article was made possible by grant number ES 00628 and ES05707 from the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health. Its contents are solely the responsibility of the author and do not necessarily represent the official views of the NIEHS.

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