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INHALATION TOXICOLOGY: IV. TIMES TO INCAPACITATION AND DEATH FOR
RATS EXPOSED CONTINUOUSLY TO ATMOSPHERIC HYDROGEN CHLORIDE GAS

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16. Abstract

Laboratory rats were exposed continuously to measured atmospheric concentrations of hydrogen chloride (HCl) gas until they expired. The exposure time required to produce lethality was measured, as was the time at which physical incapacitation occurred. Incapacitation was defined operationally as loss of the ability to walk in a motor-driven wheel. These two endpoints, time-to-incapacitation and time-to-death, were equated to atmospheric HCl concentration by statistically derived regression equations. The possible relationship between the effective toxic doses of HCl gas for rats and those reported for humans is discussed.

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INHALATION TOXICOLOGY: IV. TIMES TO INCAPACITATION AND DEATH FOR
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INTRODUCTION.

    The recognition that toxic components of smoke are principal factors
contributing to lethality in aircraft fires is well established. To date,
however, research in this area has been concerned primarily with the
contribution made by only two of these components; namely, carbon
monoxide (CO) and hydrogen cyanide (HCN). These two gases have been
classified by toxicologists as examples of "systemic" toxicants, a rather
imprecise but commonly used term. An additional class of toxicants found
in smoke is referred to simply as "irritant" gases.

    Hydrogen chloride (HCl) is the most commonly recognized member of the
irritant gas family. It is the major decomposition product of many halogen-
ated polymers used in aircraft today--polymers such as polyvinyl chloride
(PVC) and polychloroprene, used in electrical wiring insulation, cabin
wall and ceiling panels, seats, fabrics, etc.

    Hydrogen chloride gas is extremely soluble in water, forming hydro-
chloric acid. It is very reactive chemically, highly irritating and
inflammatory to all biological tissue, and quite corrosive to most metals.
It has an Occupational Safety and Health Administration (OSHA) industrial
exposure ceiling (never exceed) of five parts per million (ppm) (17). A
1-hour exposure to 100 ppm has been said to be the tolerance limit for
humans (6,9); more severe exposures may result in laryngeal spasms or
pulmonary edema, according to Dyer and Esch (9). The same authors docu-
mented the delayed complications (dyspnea, chemical pneumonitis, and death)
from HCl exposure in a study of 175 firefighters who were exposed to smoke
from PVC fires.

    Historically, HCl gas has been recognized as a hazard to industrial
personnel, particularly during its manufacture and its use in the etching
and electroplating industries (9). In 1942, Machle et al. (11)
exposed rabbits and guinea pigs to HCl concentrations from 30 ppm to
12,300 ppm for time periods of 5 minutes to 120 hours. They noted that a
30-min exposure to 3,900 ppm HCl produced 100-percent mortality within
2 months postexposure, as did exposure to 660 ppm for 2 or more hours.
They concluded that the upper limit of safety for long exposures was
about 30 ppm. This concentration (30 ppm) was shown by Cralley (2) to inhibit
ciliary activity in excised rabbit trachea following a 10-min exposure.
Barrow and coworkers (1) explained the mechanism of HCl sensory irritation
as a reaction with functional chemical groups in the membrane of trigeminal
nerve endings lining the nasal passages.

More recently, research interest has focused on the short-term response from brief exposures to HCl-containing combustion products (smoke). The current widespread use of chlorine-containing synthetic materials has prompted toxicological research in such diverse areas as synthetic fuels (5,18), construction and insulation materials (7,13,16), electrical insulation (3), and our primary interest, aircraft construction and furnishing materials (8,9).

In the mid-1970's, Federal Aviation Administration (FAA) scientists evaluated 75 in-use aircraft cabin interior materials, including several containing chlorinated polymers, for toxic gas emissions (14) and the resulting inhalation toxicity to rats (4). All the chlorine-containing materials released HCl when burned.

The extreme solubility of HCl gas in water has presented a serious problem to scientists who have attempted to maintain constant atmospheric concentrations for animal exposure experiments. Machle (11) reported it was impossible to prevent a rapid fall in HCl concentration when the relative humidity was above 25 percent, due to HCl dissolving in the condensate on the walls. Other scientists, including ourselves, have found it necessary to utilize dynamic flow systems with relatively high flow rates in order to maintain reasonably stable concentrations (5,8,10,18). Even under these conditions, whole-body exposures using multiple animals result in marked variations in the "equilibrium" concentrations attained, dependent in part on the number of animals in the exposure chamber. Absorption/solution of HCl in fur, exhaled moisture, and expelled urine necessitates frequent analysis of the chamber atmosphere if an accurate measure of exposure concentration versus time is desired.

The toxicity of inhaled HCl, as an individual agent, is not well defined. One problem is with the definition of a lethal "dose." Two experimental techniques have been used to obtain such values, and the lethal inhalation doses so obtained differ both in value and in applicability. In one approach, an animal is exposed continuously to a defined concentration of HCl until death occurs; in the other, the animal is removed from the HCl atmosphere after a defined exposure interval and dies a few days (to several months) later. The HCl doses in the two cases obviously are going to differ, but valid arguments may be made for the significance of each approach depending on the ultimate application of the data.

A second problem of definition arises if one is interested, not in lethal doses, but in exposures that produce incapacitation sufficient to prevent one's escape from a fire. For studies with laboratory animals, loss of the ability to carry out a defined function, or sequence of functions, can be evaluated. With human subjects, endpoints are more apt to be based on performance decrements, discomfort, irritation, pain, or intolerance. However, the exposure to an irritant gas considered to be "intolerable" by a human volunteer who is free to terminate his or her exposure might impede, but not necessarily prevent, the same individual from escaping a burning aircraft cabin when the likely alternative is considered. So, with animal subjects one cannot measure the more subjective contributions to incapacitation; with human subjects one dares not continue exposure to the point of actual collapse.

In order to define the levels of HCl exposure necessary to produce (i) physical incapacitation and (ii) death in the laboratory rat, we conducted the following study. Rats were exposed to a selected range of HCl concentrations (2,000 to 100,000 ppm) while enclosed in an electrically powered rotating cage assembly. The elapsed time from initiation of the exposure until the animal could no longer perform the coordinated act of walking in the rotating cage was recorded as the time-to-incapacitation (t_i). Time-to-death (t_d) was recorded (with cage rotation stopped at t_i) when visible signs of respiration ceased. An equation was then derived for each endpoint that related response time to HCl concentration.

MATERIALS AND METHODS.

Animals. Male albino rats, Sprague-Dawley strain, were acquired from Charles River Laboratories, Wilmington, MA. On receipt they were inspected by a veterinarian and housed in isolated quarters for 10 days with food and water available continuously. When ready for use, the animals were fasted overnight, weighed, and placed in separate compartments of the rotating cage.

Exposure chamber. The chamber used in this study has been described in detail previously (4). Briefly, it is a polymethylmethacrylate (PMMA) box, 25.4 by 22 by 22 cm, equipped with an internal motor-driven PMMA cage rotating at 6 rpm. This cylindrical cage, similar to an exercise wheel, is 20 cm in diameter and 22 cm long and is covered with a polypropylene screen of 1/3-inch mesh. There are three compartments in the cage, designed to accommodate one animal each. Two interior fans ensure rapid and efficient mixing of the chamber atmosphere with the incoming gas.

HCl gas handling and analysis. Anhydrous HCl gas (technical grade, Matheson Gas Products, East Rutherford, NJ) was delivered through a corrosion-resistant pressure regulator (Matheson model B16A-330) connected to an all-glass rotameter; compressed air (breathing grade) was delivered at controlled pressure through a second rotameter. The two flowing gases were mixed at a glass Y-tube connected to an inlet port in a top corner of the chamber, stirred into the chamber atmosphere by the two interior fans, and then exited the chamber at a port diametrically opposite the inlet. A vinyl tube, 1.2 cm in diameter, conducted the exhausted gas behind a water screen at the rear of the stainless steel fume hood in which the entire apparatus was situated.

The chamber atmosphere was sampled at appropriate intervals during exposures by withdrawing a 50-mL aliquot of the HCl-air mixture into a 60-mL plastic syringe. The syringe tip was immediately placed beneath the surface of a beaker of deionized water, and 10 mL of water was withdrawn. Absorption of HCl into the water was ensured by shaking the capped syringe for 3 min. The aqueous sample was expelled into a Technicon AutoAnalyzer sample cup and covered to prevent evaporative loss while awaiting analysis.

The AutoAnalyzer procedure (Figure 1) was adapted from a Technicon standard method (15) for chloride analysis. Hydrogen chloride concentration was assumed to equate with chloride ion concentration; chamber air samples,
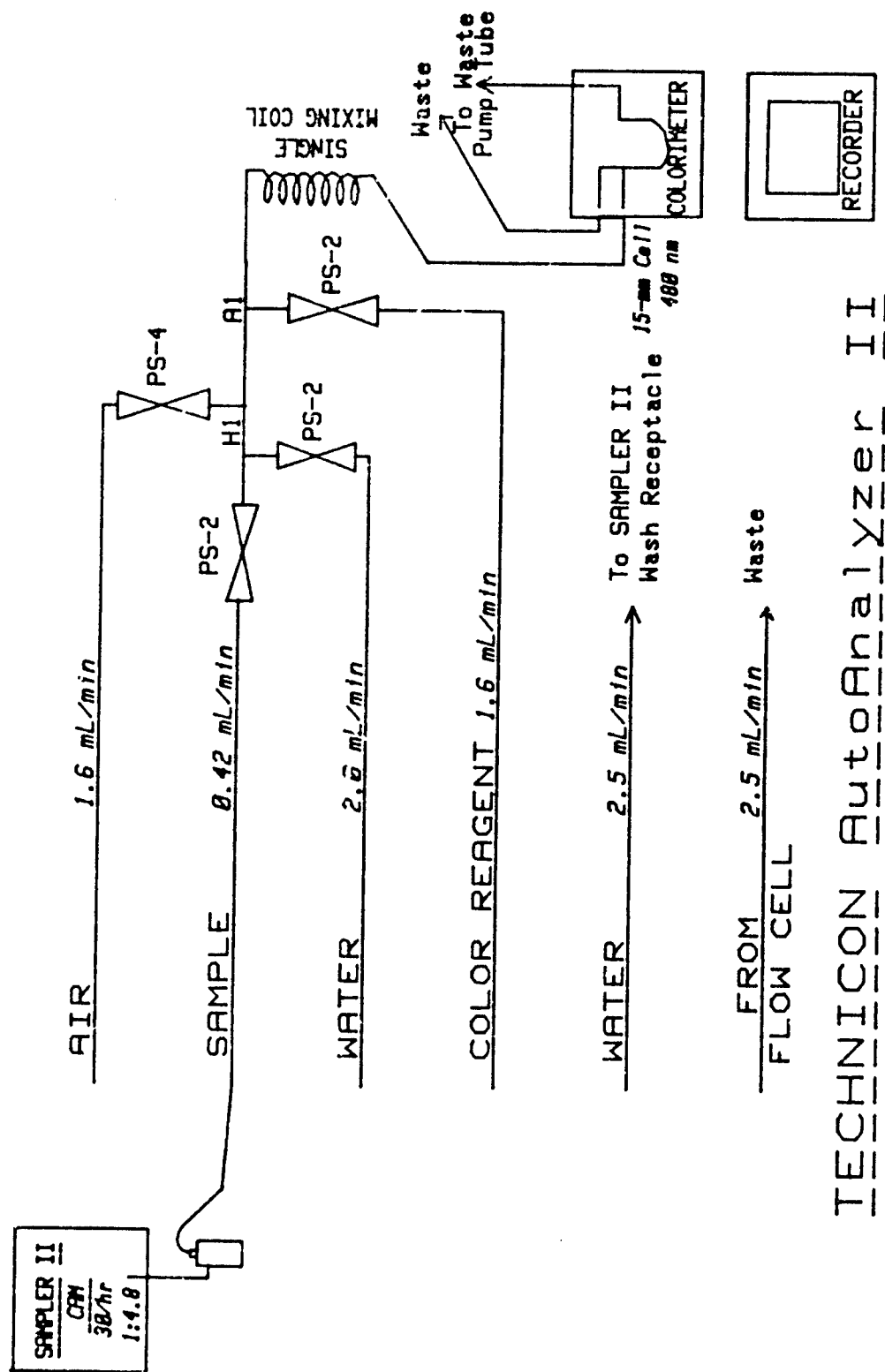
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Figure 1. Modified TECHNICON AutoAnalyzer assembly and flow diagram for chloride analysis.

in the absence of added HCl, contained no detectable chloride ion. The analytical principle is the spectrophotometric measurement, at 480 nanometers (nm), of ferric thiocyanate formed from the stoichiometric displacement of thiocyanate, by chloride, from a solution of mercuric thiocyanate in the presence of ferric ion (19).

Immediately before the analysis of each set of unknowns, a series of chloride standards, in the concentration range of 50 to 4,500 micromoles/L, was analyzed, and the results were used to calculate a standard response curve. These working standards were routinely prepared from dilutions of a standardized sodium chloride solution. (Initially, the sodium chloride solutions were compared with standard chloride solutions, prepared from constant-boiling hydrochloric acid and from primary standard grade potassium chloride, to verify that both the acidic and neutral chloride solutions gave identical color responses--which they did.)

The spectrophotometric absorbance (Abs) of the ferric thiocyanate is not a linear function of chloride concentration over the entire 50- to 4,500-micromole/L range; so the standard curve was calculated as a regression equation, using the working standard results:

$$y = a + bx + cx^2,$$

where: y is chloride ion concentration, in micromoles/L,

          x is the measured absorbance, and

          a, b, and c are the least squares regression coefficients.

Chamber concentrations of HCl gas were expressed in ppm by volume (ppm, v/v) at mean ambient temperature (25 °C) and atmospheric pressure (730 mm Hg). A typical calculation for converting chloride concentration in the aqueous sample to HCl concentration in chamber air would be:

$$[HCl] = [Cl^-] \times \frac{1000}{50} \times \frac{10}{1000} \times 22.4 \times \frac{760}{730} \times \frac{298.1}{273.1} =$$

$$= [Cl^-] \times 5.091,$$

where: [HCl] is chamber concentration in ppm (v/v),

          [Cl$^-$] is sample chloride concentration in micromoles/L,

          22.4 is molar gas volume at STP, in L/mole, and

$\frac{1000}{50} \times \frac{10}{1000}$ are dilution factors.

Exposure procedure. Airflow through the chamber, from the compressed, breathing air supply, was maintained at 12 L/min for all experiments. Flow rate from the HCl tank was selected to give the desired chamber concentration when mixed with the airflow, based on preexposure trials. The steady-state concentration that developed in the chamber, in the presence of animals, was always less than the incoming concentration.

With the fasted, weighed rats in their respective segments of the rotating cage, the chamber was sealed and cage rotation was begun. The mixing fans were turned on; the flowing HCl-air mixture, previously calibrated, was diverted into the chamber inlet; and the timer was started (t_o).

Samples of chamber atmosphere (50 mL) were taken manually at 0.5, 1.5, 3, 5, and 8 min, and at 4-min intervals thereafter throughout the exposure. The elapsed time (t_i) was noted at which the animals could no longer walk in a coordinated fashion in the cage, and at this point rotation was stopped. Observation continued until visible signs of respiration ceased, at which time t_d was recorded for each animal.

"Dose" response calculations. Using the calculated values from the AutoAnalyzer assays, a plot of HCl concentration versus exposure time was constructed. The integrated areas under this curve from $t = t_o$ to $t = t_i$ and from $t = t_o$ to $t = t_d$ were calculated for each animal, and these (concentration x time) products were designated Ct_i and Ct_d respectively. (This Ct-product can be viewed as a quantity that is related to the inhalation dose received by each animal, depending in part on how constant the animal's minute respiratory volume (MRV) is during the exposure.)

An "average" exposure concentration was calculated as the quotient of the Ct-product divided by the time to the particular response; i.e., t_i or t_d. An equation relating response time to exposure concentration was generated by the Marquardt procedure (12) for least squares estimation of nonlinear parameters.

RESULTS AND DISCUSSION.

The precision of the HCl assay procedure, documented by assaying six replicate samples each of 14 concentrations (50 to 4,500 micromoles/L), is quite good; the standard deviation for the 14 sets of six measurements averaged 0.002 Abs and the coefficient of variation averaged less than 3 percent. A plot of Abs versus concentration for these 84 chloride standards, as well as the least squares regression curve, can be found in the Appendix as Figure A1.

Figure 2 is a plot, for a representative experiment, of the assayed HCl concentration as a function of exposure time, with t_i and t_d indicated. In this experiment, t_i was 32 min and t_d was 33 min. The integrated area under the curve from $t = 0$ to $t = 32$, which would be $C \cdot t_i$, is indicated as the hatched area and is numerically equal to 471,993 ppm·min. The average HCl concentration, calculated as the quotient, $C \cdot t_i / t_i$, is 14,750 ppm.

Variations in HCl concentration in the chamber atmosphere are evident in Figure 2 and were typically observed in all exposures, despite a flow rate of one chamber volume per minute. The increase in concentration that begins at about 12 min could reflect saturation of the fur and moist surfaces of the animal with HCl and thus a decreased rate of removal from the atmosphere. A significant drop in concentration, such as occurred during the 20- to 24-min interval, was a typical feature of all experiments
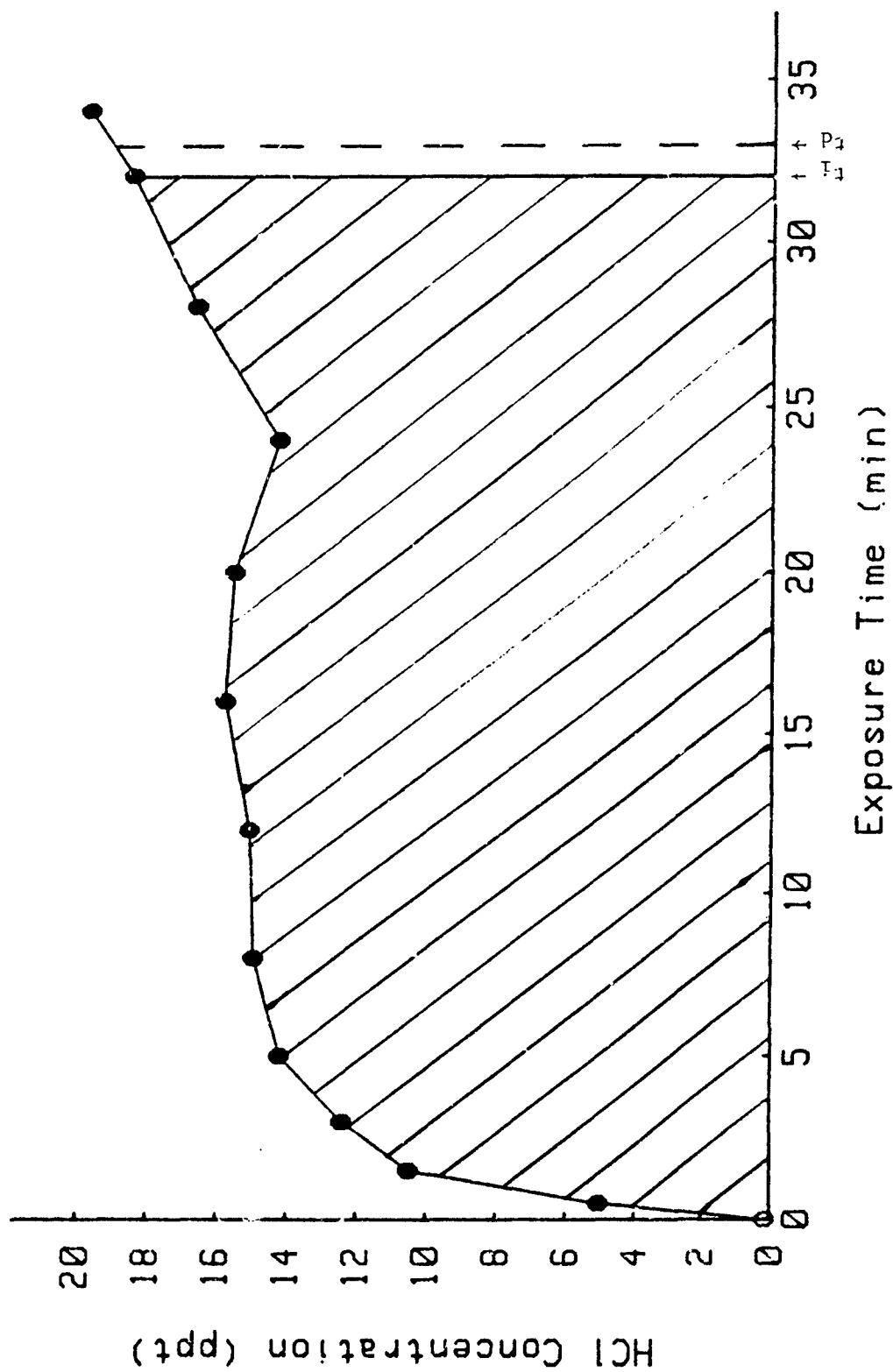
Figure 2.   HCl concentration in chamber atmosphere as a function of time.
(Data are from a representative experiment; concentration is in parts per
thousand; time is in minutes; hatched area indicates integrated area (Ct_i-product,
ppt·min) from $t=0$ to $t=t_i$.)

and coincided with urination/defecation; it obviously represents the rapid absorption of HCl by these excretory products. The increased slope of the concentration curve toward the end of the exposure was also a common observation and usually coincided with gasping and hyperactivity in the subjects due to an obviously severe decrease in pulmonary ventilation, often borne out by the loss of pink coloration (cyanosis) in the extremities.

Times-to-incapacitation were measured for 43 animal exposures and times-to-death for 42 animals. These response times, the corresponding Ct-products, and the calculated average HCl concentrations are listed in Table Al in the Appendix. The relationship between response time and HCl concentration is shown in Figure 3 for the incapacitation endpoint and in Figure 4 for lethality.

The choice of a rectangular hyperbola, $y = a + k/(x-b)$, as the mathematical form for the statistically derived regression equation seemed an obvious one, because that mathematical relationship corresponds to the physiological one between dose and the response to a toxic insult. The translated axes, which now represent the asymptotic values for the two variables, correspond to the theoretical threshold concentration for the selected toxic endpoint and to the irreducible time to achieve that effect by an overwhelming concentration of toxicant.

The least squares regression equation for incapacitation is

$$t_i = 3 + 336/(HCl-0.3),$$

where: t_i is in minutes and

HCl concentration is in parts per thousand (ppt).

The constants, a=3 and b=0.3, in the physiological interpretation of the equation, suggest that the threshold concentration of HCl that would just produce incapacitation following an _infinitely_ _long_ exposure period would be 300 ppm (0.3 ppt) and that the shortest t_i that could be obtained from an infinite exposure concentration would be 3 minutes. These values seem to be reasonable projections (as limiting values) of the results of our experiments, wherein an average HCl concentration of 94,000 ppm produced a t_i of 5.5 min and a 2,000-ppm exposure gave a t_i of just over 3 hours (185 min). Analogous comments are applicable to the resultant equation for lethal endpoints:

$$t_d = 3 + 411/(HCl-0.4).$$

This equation for a hyperbola, which was used to describe the experimental results, can be linearized in two different ways, once the parameters, a and b, have been assigned values. One approach is a log-log plot, which for the incapacitation endpoint would be a plot of $\log(t_i-3)$ versus $\log(HCl-0.3)$; such a plot is depicted in Figure 5. A second linearizing transformation is illustrated by Figure 6 for the lethality data, wherein the reciprocal of (t_d-3) is plotted against $(HCl-0.4)$.
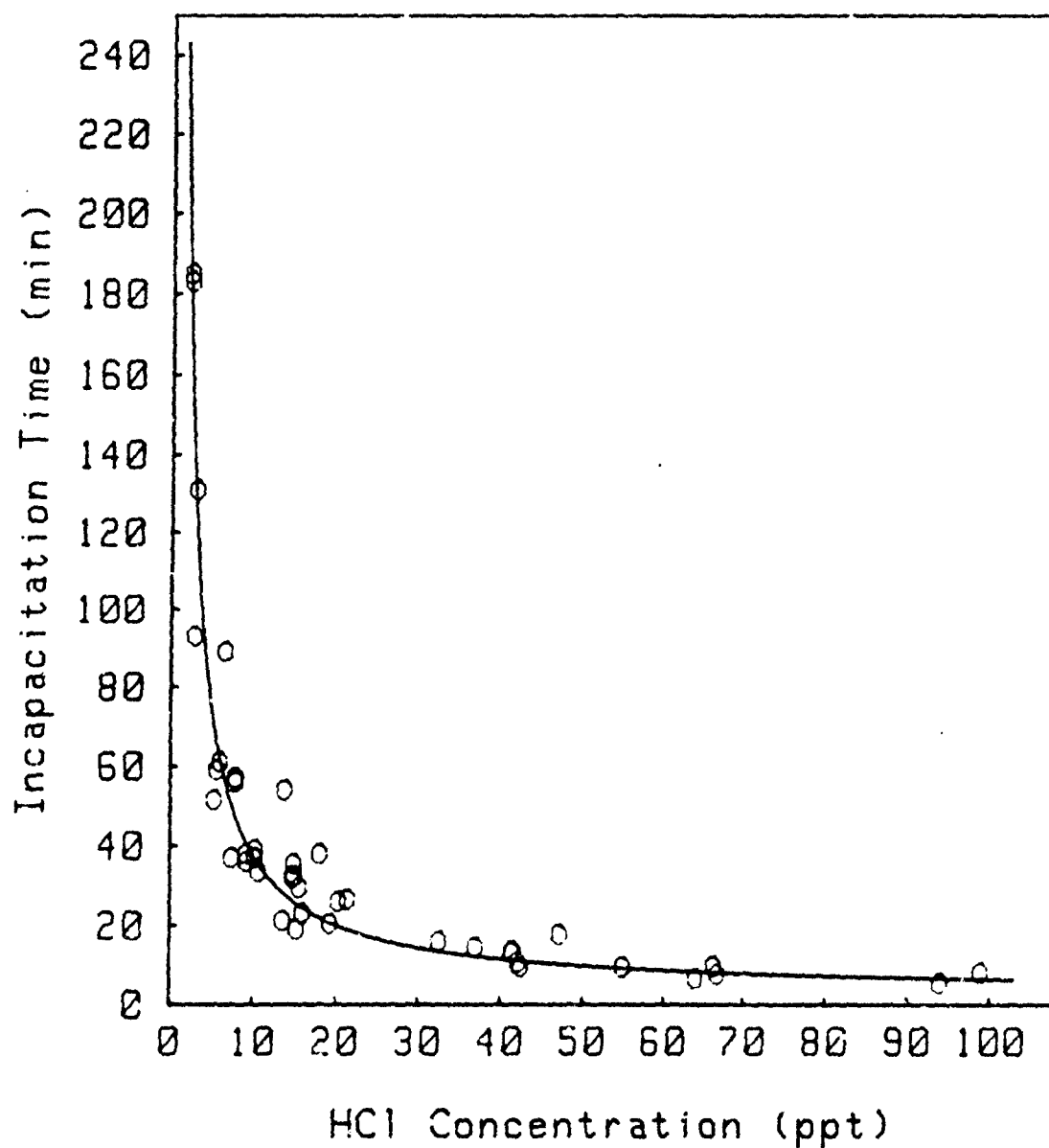
Figure 3.   Incapacitation time as a function of HCl concentration.   (N=43, time is in mimutes, concentration is in parts per thousand; regression parameters: correlation coefficient=0.96, standard error of estimate=11.2, 95% confidence interval for the constant, 336, is 314 to 358.)
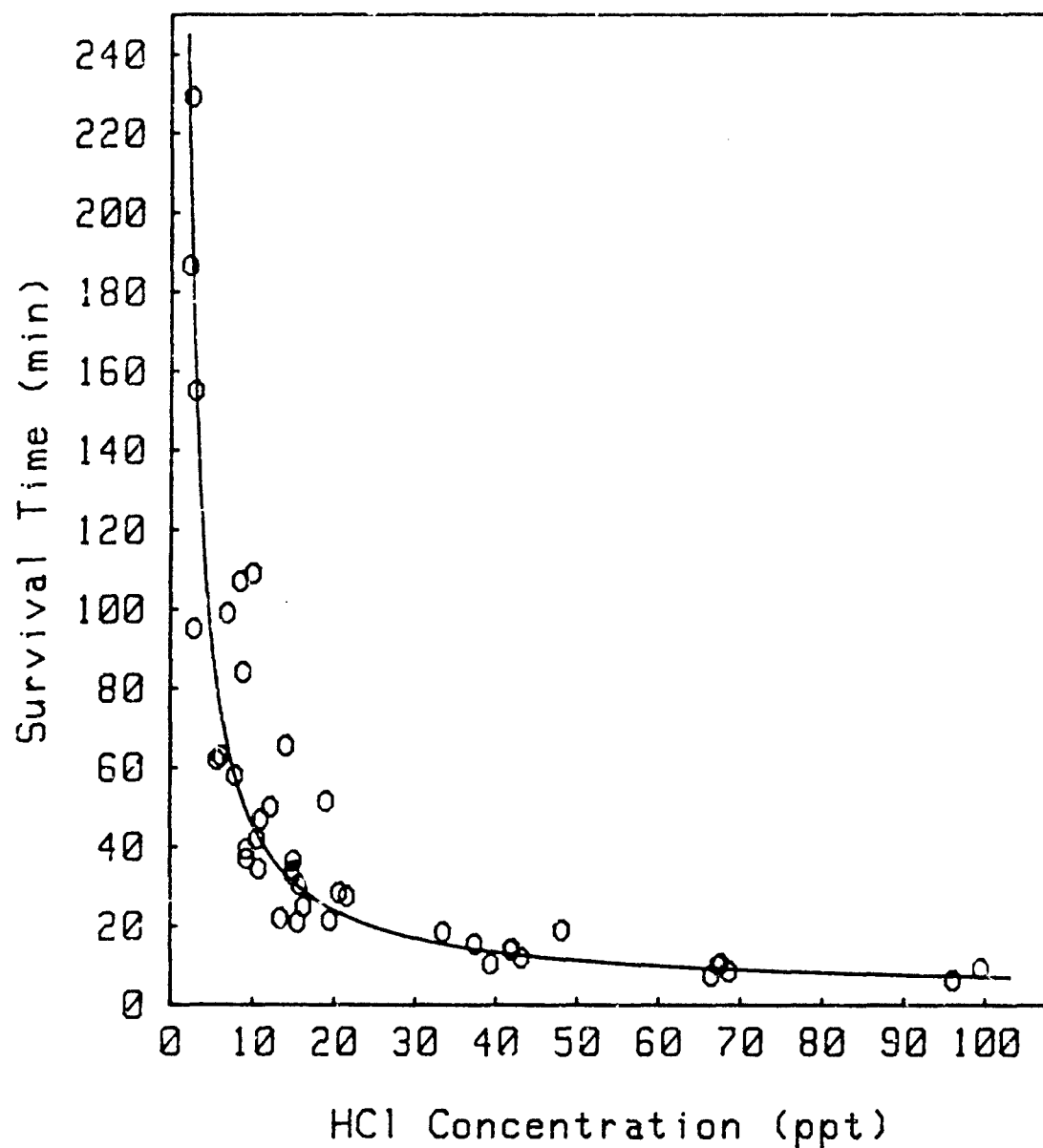
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Figure 4. Survival time as a function of HCl concentration. (N=42, time is in minutes, concentration is in parts per thousand, exposure was continuous at the indicated concentration until the animal expired; regression parameters: correlation coefficient=0.92, standard error of estimate=22.0, 95% confidence interval for the constant, 411, is 364 to 474.)
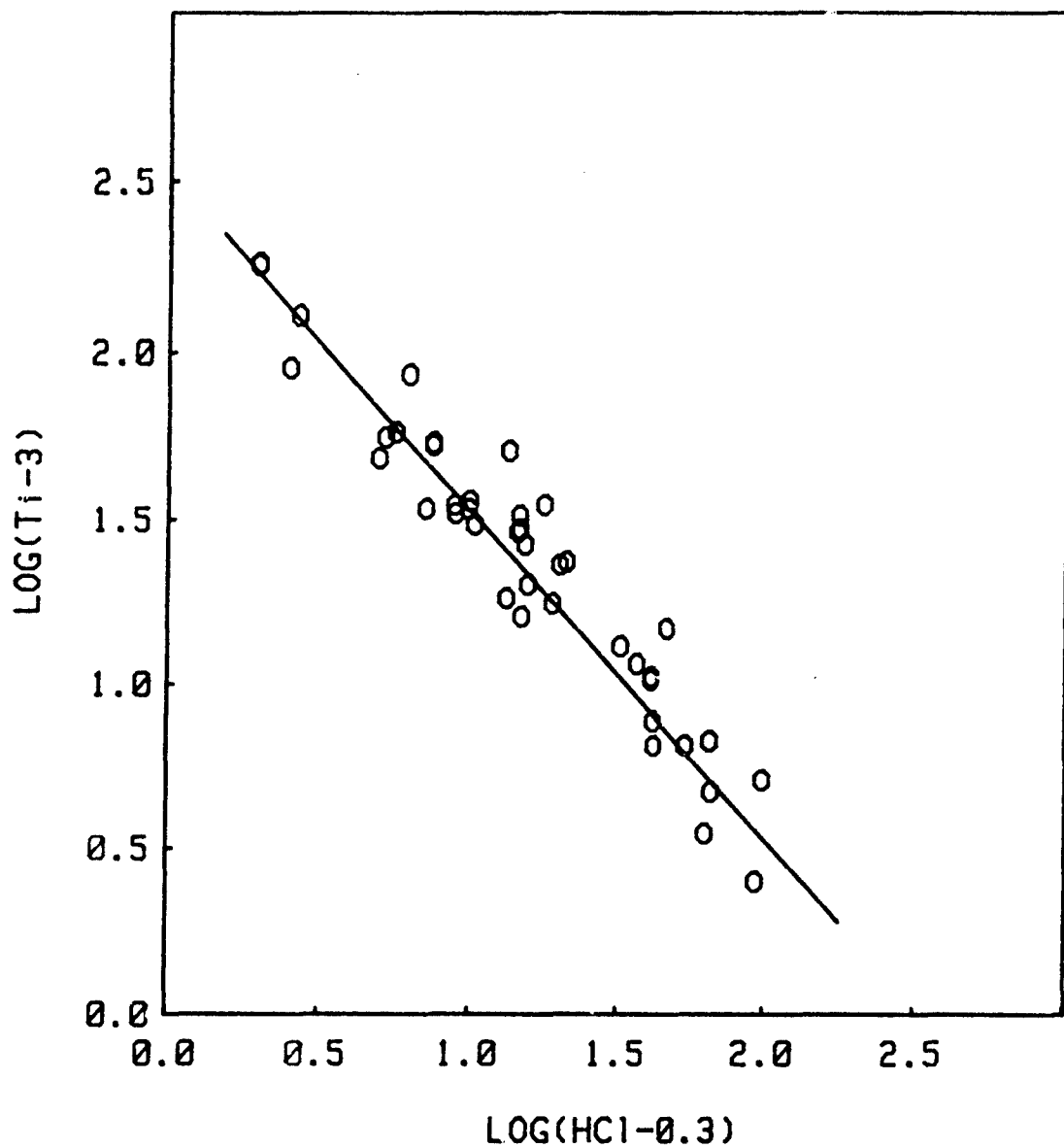
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Figure 5. Log-log plot of (t_i-3) versus (HCl-0.3), a linearized form of the equation relating response time to concentration. (N=43, time is in minutes, concentration is in parts per thousand, regression correlation coefficient=0.96.)
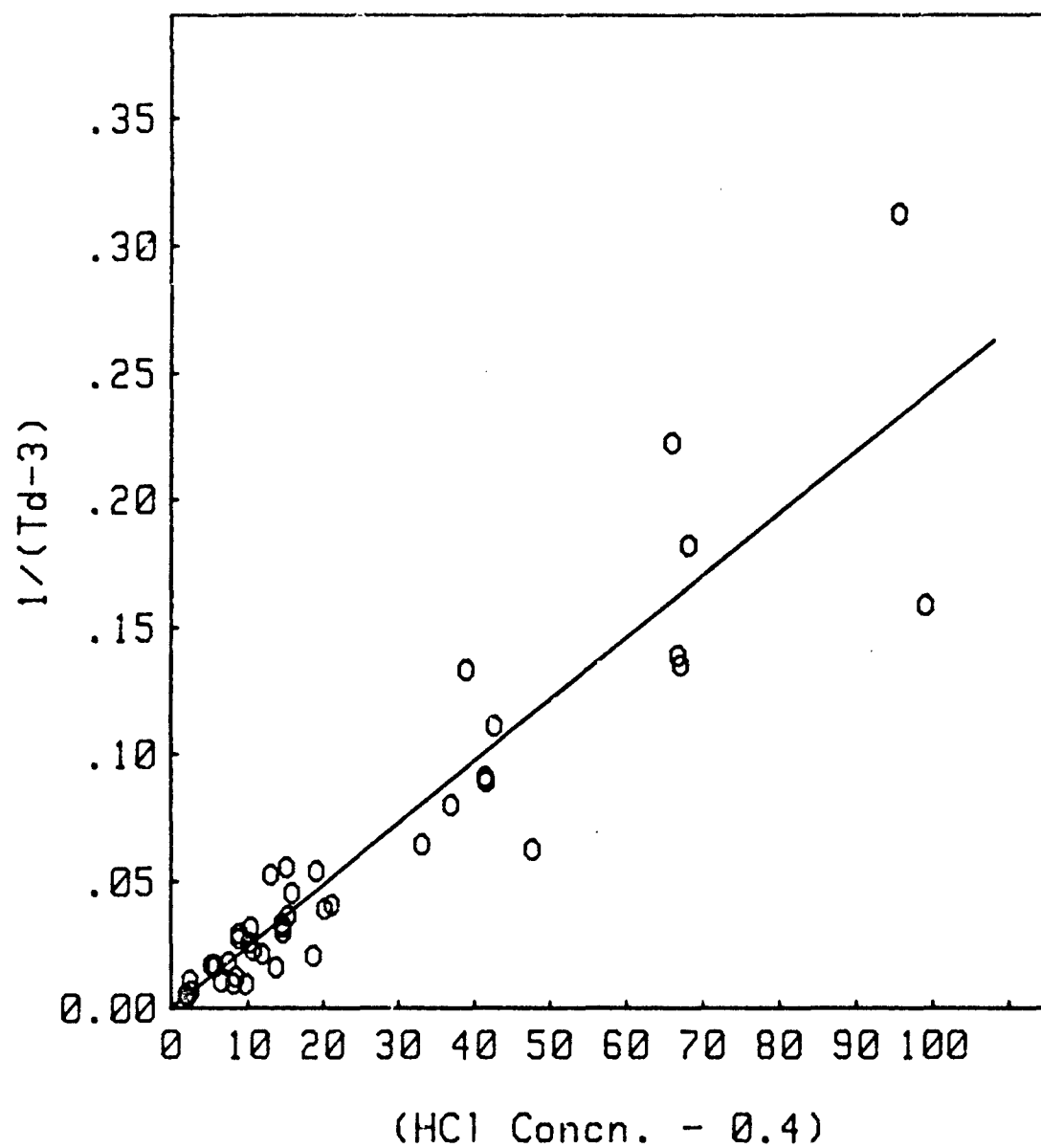
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Figure 6. Reciprocal response-time as a function of HCl concentration. (N=42, time is in minutes, concentration is in parts per thousand, regression correlation coefficient=0.92.)

There is obviously some scatter in the measured values of time-to-response, which increases in absolute value--as one would predict--with decreasing HCl concentration. This is most readily observed in Figures 3 and 4; the seemingly large variation in t_d that occurs at higher HCl concentrations in Figure 6 is an artifactual exaggeration that has been introduced by the use of reciprocal response time as a plotting variable. The regression curves are, from visual inspection of the figures, reasonable and useful reflections of the relationship between concentration and response time. The statistical measures of the "goodness of fit" are listed in the legends of the individual figures for the pertinent regression parameters.

The magnitude of the HCl concentration required to produce incapacitation (and/or death) was significantly greater than the authors had expected based on statements found in the scientific literature. Machle et al. (11) had reported lethal Ct-products of 72,000 ppm·min for rabbits and guinea pigs; Barrow et al. (1) have stated that 3,090 ppm·min would be incapacitating for humans while other sources (6,9) suggest limits below 10,000 ppm·min, while in the present study the Ct-product averaged about 500,000 ppm·min.

The mechanism of action for HCl toxicity in rats, based on observations during this study, seems to be primarily one of mechanical suffocation. This suffocation seems to be the result of mechanical blockage of the upper airways (nasopharyngeal) caused by the extreme inflammatory and corrosive action of this strong mineral acid on these tissues. Postmortem examination (gross pathology, performed by forensic pathologist W. R. Kirkham, M.D., Ph.D.) indicated surprisingly little damage to airways below the trachea, but almost total destruction from pharynx to nares.

The major significance of this study is that, for the first time, we have data that relate animal response times to HCl concentrations as a continuous function over significant time and concentration spans. Until this study, which was conducted in 1980, no information was available that measured incapacitation as a function of concentration; and lethality data were available only as LC_{50} values, and then only for specified exposure times; e.g., a 30-min LC_{50}, a 2-h LC_{50}, a 6-h LC_{50}, etc. (If one has values for 30-min and 6-h LC_{50}'s, how does one find the 3-h LC_{50}?)

Our concern about the difference between the results of this study and literature suggestions for the incapacitating/lethal doses of HCl for humans prompted the FAA to sponsor research to ascertain the effects of HCl exposure for a nonhuman primate species. The published results of that study (10), at Southwest Research Institute, indicate that the HCl exposure necessary to incapacitate baboons was at least 10 times greater than literature values suggested for humans.

The significance of that support, from experimental data using primates, for the rodent data reported in this study is that it strengthens the suspicion that literature values for humans are possibly just overly conservative estimates--estimates that may have been based on (dis)comfort indices as endpoints, rather than actual incapacitation. Therefore, HCl in smoke from natural fires may contribute less to incapacitation, and thus to failure to escape the fire, then had been previously assumed.

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SUMMARY AND CONCLUSIONS.

Rats were exposed in the Civil Aeromedical Institute (CAMI) inhalation toxicity assay system to selected atmospheric concentrations of HCl gas in air; these concentrations ranged from 2,000 to 100,000 ppm. The CAMI system utilizes an enclosed rotating wheel that allows the measurement of a physical incapacitation endpoint as well as the traditional one of lethality. These two endpoints were measured time-to-incapacitation (t_i) and time-to-death (t_d); observed response times ranged from 5.5 to 229 minutes. Results were plotted as scatter plots (response time versus HCl concentration), and then regression equations were fit to each data set using a nonlinear least squares technique.

The resulting response equations are:

$$t_i = 3 + 336/(HCl-0.3) \text{ for incapacitation and}$$

$$t_d = 3 + 411/(HCl-0.4) \text{ for lethality,}$$

where response times are in minutes and HCl concentrations are in parts per thousand.

These results suggest that HCl, in smoke from natural fires, would not be nearly so incapacitating as had been previously thought, with concentrations necessary to produce incapacitation in 10 minutes possibly being as much as 10 times greater than those suggested by the scientific literature.

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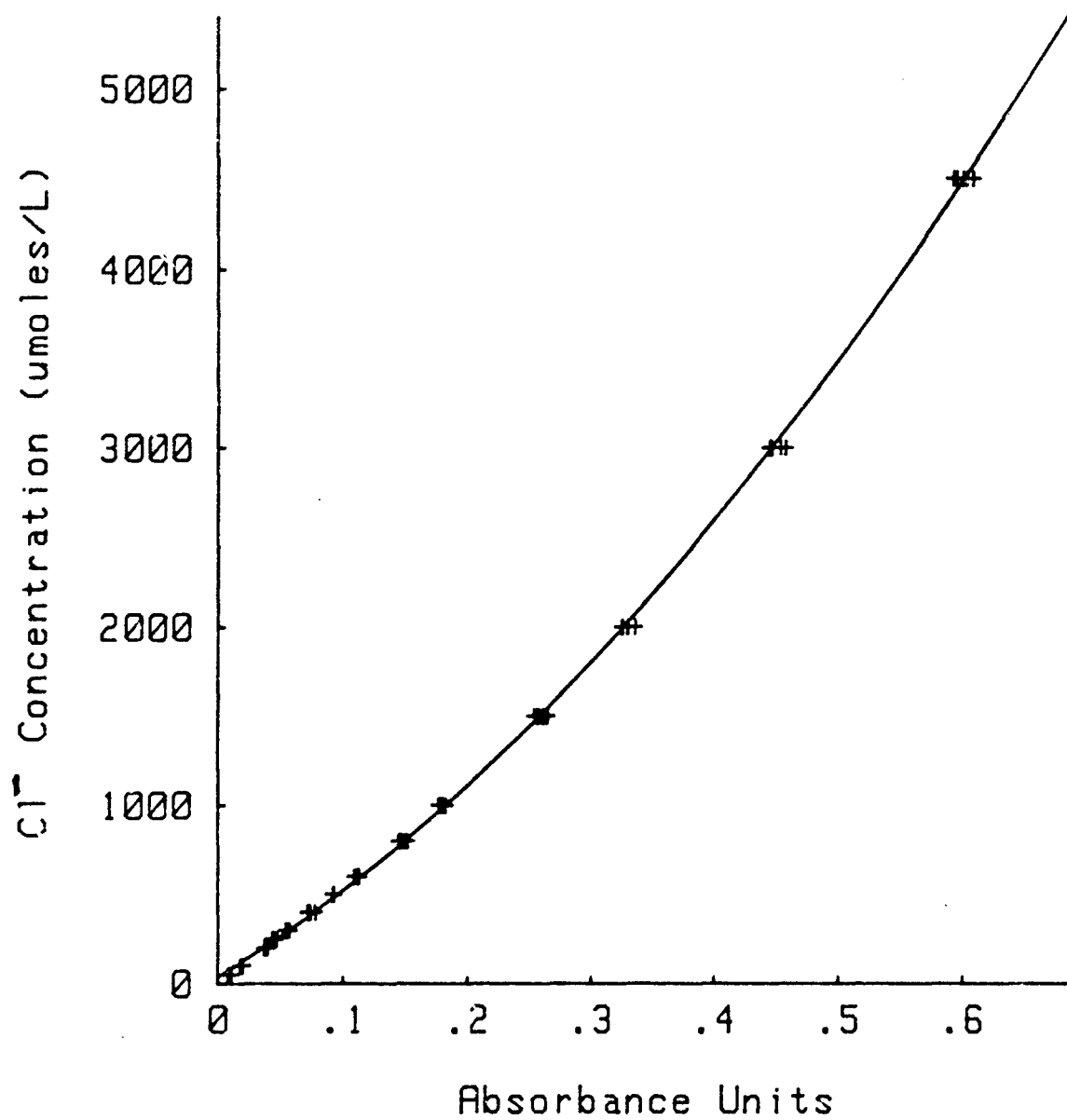
APPENDIX

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Figure A1. Standard curve: Chloride ion concentration as a function of absorbance at 480 nm.
Regression equation: $y = 37.7 + 4329x + 5156.4x^2$;
correlation coefficient = 0.999.

TABLE A1

RESPONSE TIMES AND HCl CONCENTRATIONS*

t_i, min	$C \cdot t_i$, ppt·min	HCl, ppt	t_d, min	$C \cdot t_d$, ppt·min	HCl, ppt
5.5	516.8	94.0	6.2	595.1	96.0
6.5	416.3	64.0	7.5	497.9	66.4
7.7	514.6	66.8	8.5	582.7	68.5
8.1	801.1	98.9	9.3	924.7	99.4
9.5	403.2	42.4	10.2	685.1	67.2
9.5	521.7	54.9	10.4	701.9	67.5
9.5	521.7	54.9	10.5	412.8	39.3
9.7	643.7	66.4	12.0	517.1	43.1
9.7	643.7	66.4	14.0	585.5	41.8
10.7	450.4	42.1	14.2	596.1	42.0
13.3	549.2	41.3	15.5	579.1	37.4
13.5	559.5	41.4	18.5	619.0	33.5
14.5	535.3	36.9	19.0	913.6	48.1
16.0	519.8	32.5	21.0	325.9	15.5
17.7	834.5	47.1	21.5	418.5	19.5
19.0	289.6	15.2	22.0	294.6	13.4
20.5	395.2	19.3	25.0	406.1	16.2
21.2	288.0	13.6	27.5	592.9	21.6
23.0	367.2	16.0	28.5	586.7	20.6
26.0	528.8	20.3	30.5	480.1	15.7
26.5	567.5	21.4	33.0	490.7	14.9
29.5	459.2	15.6	34.0	513.0	15.1
32.0	472.0	14.7	34.5	371.7	10.8
32.5	486.7	15.0	36.5	549.8	15.1
33.5	356.3	10.6	37.0	343.0	9.3
35.5	531.1	15.0	39.5	365.7	9.3
36.0	332.4	9.2	42.0	442.1	10.5
37.0	376.0	10.2	47.0	521.5	11.1
37.0	275.2	7.4	50.0	612.2	12.2
38.0	685.4	18.0	51.5	980.7	19.0
38.0	348.4	9.2	58.0	456.3	7.9
39.0	400.9	10.3	62.0	348.1	5.6
51.5	272.7	5.3	63.0	385.6	6.1
54.0	745.5	13.8	65.5	922.0	14.1
56.0	439.4	7.8	84.0	740.7	8.8
57.0	447.5	7.9	95.0	269.6	2.8
59.0	326.7	5.5	99.0	684.6	6.9
61.0	364.0	6.0	107.0	909.6	8.5
89.0	586.5	6.6	109.0	1100.7	10.1
93.0	263.0	2.8	155.0	464.1	3.0
131.0	393.3	3.0	186.5	426.9	2.3
183.0	416.7	2.3	229.0	589.7	2.6
185.0	422.4	2.3			

*Concentrations and C·t-products are in parts per thousand (ppt).