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Methylecgonidine Coats the Crack Particle

RONALD W. WOOD,¹ JALIL SHOJAIE, CHING PING FANG AND JOHN F. GRAEFE

Nelson Institute, Department of Environmental Medicine, NYU Medical Center, Tuxedo, NY 10987

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WOOD, R. W., J. SHOJAIE, C. P. FANG AND J. F. GRAEFE. *Methylecgonidine coats the crack particle*. PHARMACOL BIOCHEM BEHAV 53(1) 57-66, 1996. — Crack is a form of cocaine base self-administered by smoking. When heated, it volatilizes and may partially pyrolyze to methylecgonidine (MEG). Upon cooling, a condensation aerosol forms. Heating cocaine base in model crack pipes produced particles of about 1 μm in diameter, regardless of the amount heated; however, MEG concentration increased from $\leq 2\%$ at 10 mg per heating to as much as 5% at 30 mg per heating. Methylecgonidine was $\leq 1\%$ of the recovered material when cocaine was vaporized off a heated wire coil, but the particles were larger (2–5 μm), and the distribution disperse. The vapor pressure of MEG was higher [$\log P(\text{mm Hg}) = 9.994 - 3530/T$] than cocaine base, consistent with MEG coating the droplet during condensation, and with evaporation during aging or dilution. Disappearance of MEG from a chamber filled with crack smoke was a two-component process, one preceding at the rate of cocaine particle removal, and the other at the desorption rate from other surfaces. Particle diameter influences the deposition site in the respiratory tract; thus, the likely different patterns of deposition in the respiratory tract of humans and animals of crack aerosols produced by different techniques warrant consideration, as they may influence our understanding of immediate and delayed sequelae of the inhalation of cocaine and its pyrolysis product, MEG.

Crack Cocaine Methylecgonidine Particle-size aerosol Vapor pressure Drug aerosols

CRACK is a form of cocaine base self-administered by smoking. A lump of this material typically is put on a screen in a pipe and a flame drawn across it as the smoker inhales. When heat is applied to the drug, it rapidly changes state from solid to liquid to vapor. Cocaine base has a melting point of 98°C, and displays vapor pressure suitable for delivering cocaine above 160°C (12). Ignition and combustion of the material may occur at much higher temperatures, but pyrolytic degradation is more common, and commences around 170°C. As the cocaine travels away from the flame and cools, the vapor condenses forming “smoke,” which is in fact a condensation aerosol composed of cocaine base droplets and associated pyrolysis products.

The principal pyrolysis products of cocaine are methylecgonidine [anhydroecgonine methyl ester (MEG)] and benzoic acid (10,11,18,30). Methylecgonidine has been found in the urine of crack smokers (10,11). Cocaine and MEG are bases, and when inhaled they offer at least an alkaline challenge to the lung. Bronchoconstriction (21) and other pulmonary complications (24–26) are associated with crack smoking. Methylecgonidine alone also induces bronchoconstriction when inhaled (3), and has pharmacologic activity in vitro (5) and in vivo. For example, cardiopulmonary and body temperature changes have been observed after inhalation or intravenous

administration of MEG to nonhuman primates in our laboratory. Thus, the physical and chemical characteristics of the atmosphere produced by heating cocaine base warranted detailed examination.

Methylecgonidine is liquid at room temperature and has a higher vapor pressure than cocaine. The present study was undertaken in part to provide a description of the vapor pressure of MEG as a function of temperature, and to examine the pyrolyzate’s impact on “crack” aerosols. The vapor pressure of a volatile substance can be described by the relationship $\log P(\text{mm Hg}) = A - B/T$, where $P(\text{mm Hg})$ is the vapor pressure in millimeters of mercury, A and B are the intercept and slope, respectively, and T is the temperature in degrees Kelvin (12). Vapor pressure exerts an influence on the physical state of the crack aerosol both during the smoking process and with the passage of time. If the vapor pressure of a material is low enough, deposition and absorption resemble those of particles, rather than those of a vapor. If principally a particle, its aerodynamic properties determine the pattern of respiratory tract deposition, and thus, cocaine and its pyrolysis products might deposit differentially in the respiratory system (22). The achieved deposition pattern for a given aerosol in different regions of the respiratory tract is a function of the size distribution of the aerosol, usually measured as the mass median

¹ Requests for reprints should be addressed to R. W. Wood, Department of Environmental Medicine, NYU Medical Center, Longmeadow Road, Tuxedo, NY 10987.

aerodynamic diameter (MMAD), as well as the degree of dispersion of the particle distribution [geometric standard deviation (σ_g)]. The aerosols can be characterized using cascade impactors, a primary standard technique for determining particle size that relies on the inertial impaction of particles on surfaces (7,28).

The present study also compared the size and chemical composition of the crack droplets produced by simulated crack smoking in a model crack pipe with those produced with the "hot-wire" technique (6). The hot-wire technique consists of applying a known amount of cocaine base in a solvent to a coil of nichrome wire, allowing the solvent to evaporate, and heating the wire electrically while the subject inhales through an attached mouthpiece, or when a positive pressure is applied to carry the "smoke" to a laboratory animal.

METHODS

Comparison of Crack Pipe and Hot-Wire Technique

We borrowed a hot-wire generator (C. Schindler, personal communication) made by the Minnesota group (6). Briefly, this device consisted of a nichrome wire (no. 24) coil with an internal diameter (ID) of 0.3 cm. There were nine turns on the element, and the overall length of uncoiled wire was approximately 17 cm. To apply cocaine base to this coil, a solution of cocaine (100 or 300 mg/ml) was prepared using ethanol or acetone, and 0.1 ml was deposited on each coil while it was held in an inverted position. Although the acetone dried in moments, the ethanol solutions were allowed to dry for several hours, usually overnight. When dry, the coil was placed in the middle of a 9-mm-ID tube. The end of the coil was approximately 3 cm from the end of the outlet tube; the outlet tube typically would be approximately 1–2 cm from a test subject. The coil was heated by operating a switch in series with the primary of a stepdown transformer with a low output impedance, and a rectifier to provide high-amperage direct current to the coil. Air was drawn through the tube at 5 l/min, the calibrated sampling rate of the Mercer impactor (described below) used to measure the particle size distributions. Eight determinations were made under each of the conditions examined in this series of experiments.

To compare the hot-wire technique with a model crack pipe used previously (23), cocaine (100 or 300 mg/ml) was dissolved in acetone or ethanol and applied to a double stainless-steel screen in the pipe. In separate experiments, lumps of cocaine base (approximately 30 mg) were placed on the screen to simulate "street" conditions. A standard flame was applied to the screen by fixing a Bunsen burner at an angle above and to the side of the bowl. A pilot light was fixed at the tip of the Bunsen burner, and when the hose to the Bunsen burner was unclamped for approximately 5 s, a flame was applied to and surrounded the drug. An airflow of 5 l/min was drawn through the pipe, commencing a few seconds before application of the flame and continuing for a few seconds until the cocaine had disappeared. The screens and hot-wire coils were cleaned with ethanol after each use and dried with acetone.

Condensation Nuclei

When hot atmospheres that are saturated with a volatile material cool, the vapor condenses to form droplets. This can happen spontaneously, but in the presence of a flame very large numbers of very small particles of virtually no mass ("Bunsen" nuclei) provide a large surface for condensation, facilitating the formation of many smaller particles of uni-

form size. Because no source of condensation nuclei is employed with the flameless hot-wire technique, we determined whether adding condensation nuclei in the form of submicron sodium chloride crystals would reduce the median particle diameter as well as the dispersion of the distribution. To this end, sodium chloride was placed in a ceramic boat inside a tube oven at 725°C, a temperature sufficient to foster evaporation. Air was passed through the tube oven at 5 l/min, forming minute particles as it cooled to room temperature. These nuclei are $\leq 0.1 \mu\text{m}$ in diameter, estimates derived from electron microscopy. The nuclei numbered $> 10^7/\text{cc}$, measured with a condensation nucleus counter (model 3020; TSI CNC, Minneapolis, MN); because of coagulation, we estimate this concentration to be approximately $10^8/\text{cc}$.

Measurement of Particle Size Distributions by Inertial Impaction

A cascade impactor classifies particles by their aerodynamic size (7,28). A constant air flow is pulled through successively smaller orifices, thus increasing velocity and impacting particles with sufficient inertia on the surface opposite the orifice, while smaller particles follow the flow to subsequent stages. The Mercer impactor used here (model 02-170; Intox Products, Albuquerque, NM) consisted of seven impaction stages and one backup filter. The cutoff diameters for these stages were 8.1, 4.0, 2.1, 0.98, 0.5, 0.27, and $0.15 \mu\text{m}$ at 5 l/min. For the two samples taken in the chamber disappearance experiment described subsequently, a flow rate of 3.2 l/min was selected, and only five stages were inserted in the Mercer impactor, resulting in cutoff diameters of 4.87, 2.54, 1.27, 0.67, and $0.43 \mu\text{m}$.

Because a sample is collected for a range of particle sizes, cascade impactors permit the description of the concentrations of the chemical constituents of crack across particle size, in this case relying on gas chromatography to estimate mass. From the amounts of the different chemicals deposited on each stage, the MMAD and σ_g were calculated for each substance and as a total (14). This was done by linear regression performed on the probit (z -score) transformation of the cumulative mass deposited on each of the sampling stages as a function of the log of the cut size of each impactor stage.

Simulated Smoking at Higher Flow Rates

We performed experiments to reexamine the influence of flow rate on the particle size distribution as well as any discrepancy between the data presented here and those of Snyder et al. (23) using the Casella impactor. Flow rates across the wire or through the pipe for most observations were held to 5 l/min; Snyder et al. (23) demonstrated that increasing the flow from 7 to 14 l/min somewhat decreased the particle diameter; here, we report sizing data collected at 5 and 15 l/min. Snyder et al. (23) gently applied a flame to cocaine base; if any discoloration of the filter or of the material deposited in the impactor occurred, the sample was discarded. The present experiment used slightly harsher conditions that may be more representative of human self-administration on the street.

Experiments performed at 15 l/min through the pipe were conducted with the Mercer impactor sampling at 5 l/min on one leg of a Y connector, and on the other leg either a filter or a Casella impactor sampling at 10 l/min. The Casella impactor was the same one used by Snyder et al. (23), and its cut sizes at 10 l/min were computed to be 22, 3.9, 2.0, and $0.73 \mu\text{m}$ with Marple's theory (14).

Approximately 50 mg of cocaine base was put on a double

stainless-steel screen in the bowl of a 5.5-cm-diameter glass pipe similar to that used previously (23). Suction was applied to the pipe at 10 l/min. A portion of this suction, 2.5 l/min, was drawn through a Whatman GF/B glass microfiber 2.4-cm filter (Whatman Int'l, Maidstone, Kent, UK) and one or two charcoal tubes (SKC charcoal tubes, lot 120; Eighty Four, PA) in series. The charcoal tubes were used to trap any MEG vapor that might pass through the filter; the glass fiber filters collected any aerosol particles with an efficiency exceeding 99.5%. This was done six times; eight studies were conducted at 5 l/min with 30-mg lumps of cocaine base.

Chamber Disappearance Studies

To determine whether a coating and evaporation process could be detected with these materials in a situation resembling those encountered during crack smoking, 200 mg of a 1 : 3 paste of MEG and cocaine base was placed on double stainless-steel screens (40 × 40 mesh/6.45 cm²; 0.0254-cm diameter wire) in a bowl (28/15 glassware socket) attached to 24/40 glass tubes with an ID of 1.39 cm and length of approximately 60 cm, that discharged at the bottom of the 29.5-l jar. We heated the paste with a Bunsen burner while applying negative pressure to the jar at a fixed flow rate. The high concentration of pyrolysis product was used to ensure that measurable levels of pyrolysis product would persist for 15–20 min. The cocaine and MEG atmosphere was removed from the top of the "single compartment" (jar) at 2.5 l/min by pulling it through a Y connection into a glass microfiber filter, and then through two charcoal tubes in series. The alternate arm of the Y was clamped off and held the filter cartridge and tubes for the subsequent sample. A small fan was placed in the jar to mix the atmosphere; its speed was controlled with a variable transformer.

Methylecgonidine vapor was introduced by removing the "pipe bowl" and attaching a distillation arm between the 24/40 tube leading into the chamber and one neck of a two-necked, round-bottom flask into which MEG was placed. A glass tube was placed in a stopper in the other neck of the round-bottom flask with the tip below the surface of the liquid. Negative pressure was then applied at the outlet, generating bubbling and vapor saturation in the flask and chamber. The chamber was charged for approximately 30 min, a period longer than necessary to achieve a plateau concentration. Disappearance under these conditions was reported as the proportion of the first sample. To compare the disappearance of MEG from the chamber with the theoretical rate of disappearance from a single compartment of this volume and flow rate, several disappearance functions were performed with ethanol, toluene, and acetone by placing <1 ml of the solvent on the warm screen, and using the air sampling valve on the chromatograph to follow the disappearance function.

Vapor Pressure of Crack Constituents

We made several measurements of the vapor pressure of MEG at different temperatures to estimate the parameters of the vapor pressure function. We used serial saturation for this purpose (19). Several milliliters of MEG were placed in each of three small glass bottles with an internal volume of 30 ml. A stopper with two holes was placed in the top of each bottle, and the containers connected in series with glass tubing (3.73-mm ID) bent into short U-shaped segments. The inlet tube to each bottle was introduced below the surface of the liquid, so that bubbling occurred in each as negative pressure was applied at the outlet of the third bottle. The three jars

were placed in a water bath, and the temperature of the water bath varied (313, 333, 353, and 298°K). Samples were pulled through charcoal tubes to determine the atmospheric concentrations. These concentrations were converted to pressures by the gas law ($PV = nRT$) and regressed as a function of $1/^\circ\text{K}$.

Analytical Chemistry of Cocaine and Its Pyrolysis Products

A gas chromatograph with megabore capillary columns with a split injector and a flame ionization detector (HP5890A Series II; Hewlett-Packard, Sunnyvale, CA) was configured with an HP-1 methyl silicone gum column (5 m × 0.53 mm × 2.65 μm film thickness). The chromatographic conditions were helium flow: 40 ml/min; injector: 170°C; detector, 250°C; oven temperature 120°C for 30 s, ramp to 180°C at 70°C/min; plateau: 4 min. For air-sampling chromatography, the analyses were done under isothermal conditions at 60°C; the analysis interval was 20 s, and the chromatograph recycled automatically when all zones had returned to their initial temperatures. The sampling rate from the chamber through the 0.25-ml sampling loop was the same as the other conditions, 2.5 l/min.

Filter and impactor samples were promptly put in 2 ml of ethanol in 2.2 × 6 cm vials, and 0.2 ml of ethanol containing procaine as an internal standard (2.36 mg/ml) was added. No ethyl exchange esterification of cocaine or MEG occurred during storage. The vial was placed in an ultrasonic bath for approximately 3 min. For the chamber disappearance experiments, the ethanol volume was 5 ml, and the internal standard volume, 0.5 ml.

The charcoal tubes were broken in half at the foam divider, and the charcoal was shaken out, each half into a separate vial. The glass tube and glass wool for each half were added to the respective vial, using 1 ml ethanol, 1 ml carbon disulfide, and 0.2 ml of the internal standard solution. This was allowed to sit for 15 min before injection. If any materials were detected in the second half of the charcoal tube, correction for the efficiency of collection was performed.

Seized cocaine hydrochloride (Research Triangle Institute, Research Triangle Park, NC) was contaminated with traces of *cis*- and *trans*-cinnamoyl cocaine isomers. This seized material was converted to free base by heating an aqueous solution with sodium bicarbonate. The cocaine base was extracted with methylene chloride and dried over sodium sulfate. After removal of solvent under vacuum, the cocaine base was recrystallized from hexane and acetone, after stirring with activated charcoal and filtration. This afforded a white solid, melting point 97–98°C.

We prepared methylecgonidine in quantity according to the procedure of Zirkle et al. (31). The crude MEG was converted to the fumarate salt and was recrystallized from methanol and hexane to give a white solid with a melting point of 178–180°C. Benzoic acid was obtained commercially (Fisher, Springfield, NJ).

RESULTS

Comparison of Hot-Wire and Flame Techniques

Figure 1 shows two composites of photographs of the individual stages of the Mercer impactor, arranged in descending order of particle diameter: the number represents the D_{p50} , or 50% cut size for a given stage. An impactor is essentially a set of low-pass filters in series that sort particles by size, removing the largest first. The last stage is a glass fiber filter for ≤ 0.01 μm, and is not presented here. The first stages capture the

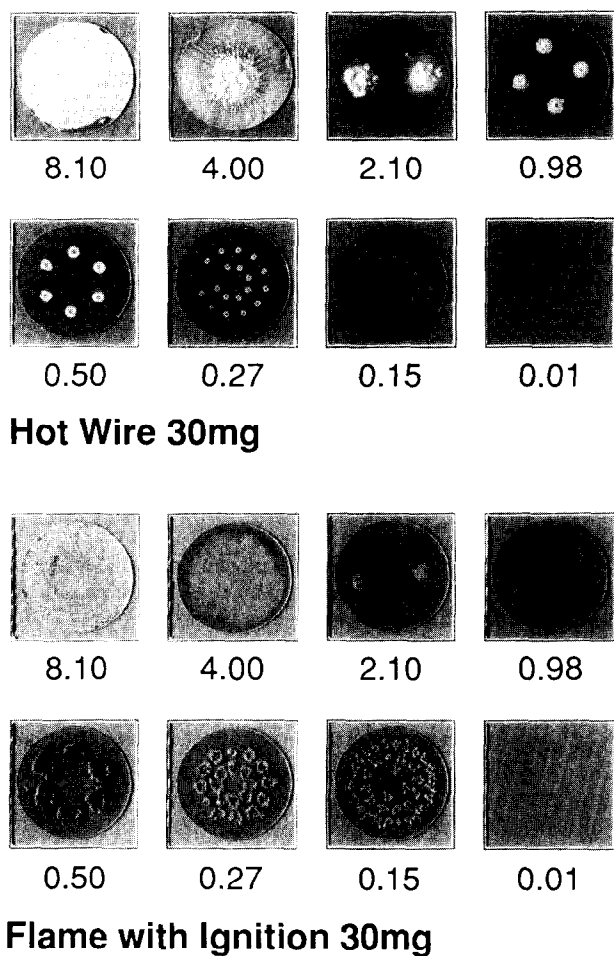


FIG. 1. Particles deposited on the seven stages of a Mercer impactor following heating cocaine with the hot-wire technique (top), or with a Bunsen burner flame in a model crack pipe (bottom). Numbers are the particle diameter cut points in micrometers for each stage. In both cases, 30 mg of cocaine base was heated. Larger particles were produced by the hot-wire technique than by the use of a flame, as during crack smoking. Pyrolysis occurred under both conditions; ignition occurred with the flame on this occasion and is evident from the black ash deposited on several stages. Actual quantification of the MMAD of particles produced by the two techniques is shown in Fig. 2.

largest particles, and sometimes a haze associated with minor amounts of vapor deposition. Note that the hot-wire technique produces large masses on the first three stages of the impactor, and lesser amounts on subsequent stages. (Under normal circumstances of particle size estimation, these stages would be considered "overloaded" and subject to some error as a result of impaction on the larger surface of the encrusted stages.)

In contrast, the flame samples with the same mass showed more deposition on the fourth and higher stages of the impactor, because of the smaller size of the particles. The color was amber to light brown in this case, except for black particles on the fourth and fifth stages of the impactor. The sample ignited as the flame was removed from the screen, and the resultant ash deposited on these two stages.

The absolute amounts of MEG, cocaine, and benzoic acid were determined by gas chromatography on each of these stages, and the MMAD and σ_g of the particle size distribution were calculated for each sample. A comparison of the hot-wire and flame generation techniques are presented in Fig. 2.

Pyrolysis did occur with the hot-wire technique, and its incidence was $<0.5\%$, as measured by summing the amounts present on the stages of the impactor (Fig. 2, top left). No vapor was detected when charcoal tubes were placed after the impactor. The relative amount of pyrolysis was low, usually $<2\%$. Increasing the mass being heated to 30 mg increased the proportion of pyrolyzate. This was most dramatic when cocaine was placed as a 30-mg lump on the screen and a torch applied. Under these circumstances, up to 5% pyrolyzate was detected using the impactor. The percent of cocaine measured with filters and charcoal tubes ($97.69 \pm 0.67\%$ (mean \pm SEM); minimum 94.4%) did not differ from that obtained using the impactor ($97.84 \pm 0.57\%$ (minimum 94.65%) (Fig. 2, top left) ($t = 0.17$, $p = 0.87$, $n = 8$). If ignition occurred, greater amber-brown discoloration of the impactor samples was evident, and two of the stages showed prominent black deposits (Fig. 1: 0.98, 0.50).

The MMAD's of MEG- or cocaine-containing particles were computed from the amounts recovered on each impactor stage; this was repeated eight times for each condition. A robust t -test based on sample medians (8) indicated that the MMADs associated with the two compounds did not differ ($t = 0.0416$, $n = 57$, $p = 0.967$); thus, we present MMADs based on the total mass. At 10 mg per trial, the flame produced a particle of about $1 \mu\text{m}$ MMAD, whereas the hot-wire technique produced a much larger particle of about $3 \mu\text{m}$ in diameter (Fig. 2, top right). The addition of sodium chloride condensation nuclei reduced the diameter of the particle generated by the hot-wire technique to about $1.8 \mu\text{m}$ (Fig. 2, top right, fifth column). This suggests that the large size of the particle resulted from the cocaine having too little surface upon which to condense; the "Bunsen" nuclei (arising from the Bunsen burner flame) provided this surface in the case of pipe smoking. Increasing the mass to 30 mg did not change the diameter of the particle produced with the flame, but did increase the diameter to about $4 \mu\text{m}$ with the hot wire. The variability of the particle size distribution tended to be greater with the hot-wire technique (Fig. 2, bottom). The mean σ_g determined for the hot-wire technique with 10 mg cocaine and added condensation nuclei was 2.31, and with the 30-mg lump volatilized with the torch, 2.47. However, when 30 mg was volatilized using the hot-wire technique, the σ_g increased to 2.96.

Simulated Crack Smoking

At 10 l/min through the pipe, the amount of cocaine recovered on the filter was 2.67 ± 0.47 mg (mean \pm SE). Thus, the efficiency of delivery from the end of the pipe was approximately 21.3%. The recovery achieved by Snyder et al. (23) under gentler conditions was $72.6 \pm 4.1\%$. The amount of MEG recovered on the filter was 0.04 ± 0.012 mg. No vapor of any type was detected on the charcoal tubes. No benzoic acid was recovered from the filters or from the bowl of the pipe. (Benzoic acid alone ignited under these conditions.) The percent of MEG of the total material emerging from the pipe stem was $1.33 \pm 0.25\%$.

High flow rates (15 l/min) through the pipe were associated with smaller cocaine particles (Table 1) than those observed at 5 l/min; the particle distributions were more disperse at the high flow rate. The extent of pyrolysis was reduced at the

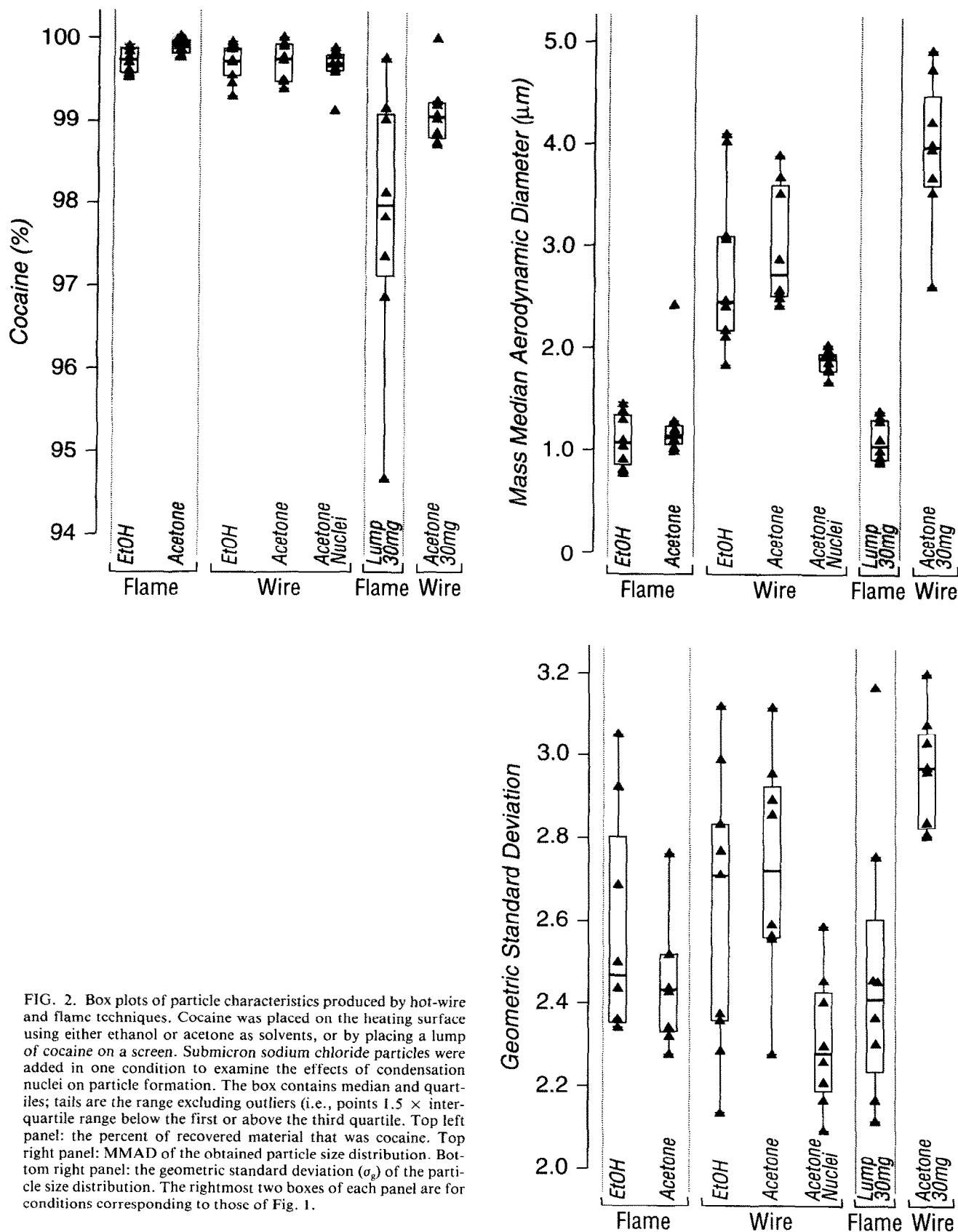


FIG. 2. Box plots of particle characteristics produced by hot-wire and flame techniques. Cocaine was placed on the heating surface using either ethanol or acetone as solvents, or by placing a lump of cocaine on a screen. Submicron sodium chloride particles were added in one condition to examine the effects of condensation nuclei on particle formation. The box contains median and quartiles; tails are the range excluding outliers (i.e., points $1.5 \times$ interquartile range below the first or above the third quartile). Top left panel: the percent of recovered material that was cocaine. Top right panel: MMAD of the obtained particle size distribution. Bottom right panel: the geometric standard deviation (σ_g) of the particle size distribution. The rightmost two boxes of each panel are for conditions corresponding to those of Fig. 1.

TABLE 1
PARTICLE SIZE DISTRIBUTION CHARACTERISTICS AND EXTENT OF PYROLYSIS
AS A FUNCTION OF FLOW RATE THROUGH A MODEL CRACK PIPE

Flow (l/min)	MMAD (μm) Mean \pm SEM	σ_g Mean \pm SEM	% Cocaine		
			Mean \pm SEM	Minimum	<i>n</i>
5	1.09 \pm 0.073	2.47 \pm 0.12	97.84 \pm 0.57	94.65	8
15	0.51 \pm 0.022	3.26 \pm 0.22	99.76 \pm 0.09	99.12	11

higher flow rate. These higher flow rates also permitted the direct and simultaneous comparison of particle size measurements using both the Mercer and the Casella impactors (23), using recomputed cut sizes. The resultant MMAD estimates for two trials were: Trial 1: Mercer: 0.92; Casella 1.15; Trial 2: Mercer: 0.91; Casella: 1.20).

Chamber Disappearance Studies

Our first attempts to describe the disappearance of cocaine and its pyrolysis products from a single compartment resulted in a slowly decreasing concentration, followed by a precipitous drop. We realized that this was because the smoke was introduced at the top of the chamber, and sampling from the bottom with no mixing. The smoke could be seen settling in the bottom of the chamber. Thus, we reversed the sites of introduction and sampling from within the chamber, and introduced a fan to ensure even mixing (Fig. 3). When the fan ran at a high speed, the particles collided with the blades or were thrown up against the walls of the chamber. The "smoky" appearance of the chamber cleared rapidly, associated with rapidly dropping cocaine levels (Fig. 4). MEG levels dropped in two phases, the more rapid of which was comparable to that of the cocaine particle. The slower phase occurred at a rate similar to that observed when only MEG vapor was introduced into the chamber. This rate of disappearance was much slower than the disappearance of several volatile liquids (ethanol, toluene, and acetone), which could not be distinguished from the theoretical single-compartment dilution kinetics modelled for these chamber volume and flow conditions: $C = 1 - [1 - e^{-Q\tau/V}]$, where Q is the flow rate, V is the total chamber volume, and τ is the time to achieve concentration C (19).

We performed a second experiment with the fan running just enough to mix the particles in the chamber. This adjustment eliminated the particles at a slightly faster rate than the theoretical rate for these chamber volume and flow conditions, but slower than that observed when the fan ran at high speed. MEG displayed a two-phase elimination process under these conditions, with the elimination rates paralleling cocaine elimination early, and becoming slower during the latter portion of the experiment (Fig. 5). The proportion of the total atmosphere composed of MEG increased later in the session. The figure presents the amounts of MEG as total, vapor, and particulate on the filter; note that during the first sample, an order of magnitude more vapor was present, and the amount on the filter was less than that observed on the second sample. Condensation of the vapor on the particles was not complete during this 1st min of sampling.

A third experiment was performed under conditions similar to the second; however, samples were collected using a Mercer impactor at 2 and 15 min following the application of flame. Figure 6 presents the proportion of MEG present on each of the stages of the impactor at both time points. The proportion

of MEG remaining on the particles decreased with the passage of time. The ratio of surface area to diameter is greatest for small particles, and smaller particles grow or shrink more rapidly during condensation or evaporation, respectively.

If MEG is coating the cocaine particle, as this implies, each coated particle will deposit both materials on the impactor surface. Because coating should be proportional to the surface area of each particle, one would expect the MMAD of the two particles to be the same, even though the mass of the two components is very different. We examined this by plotting

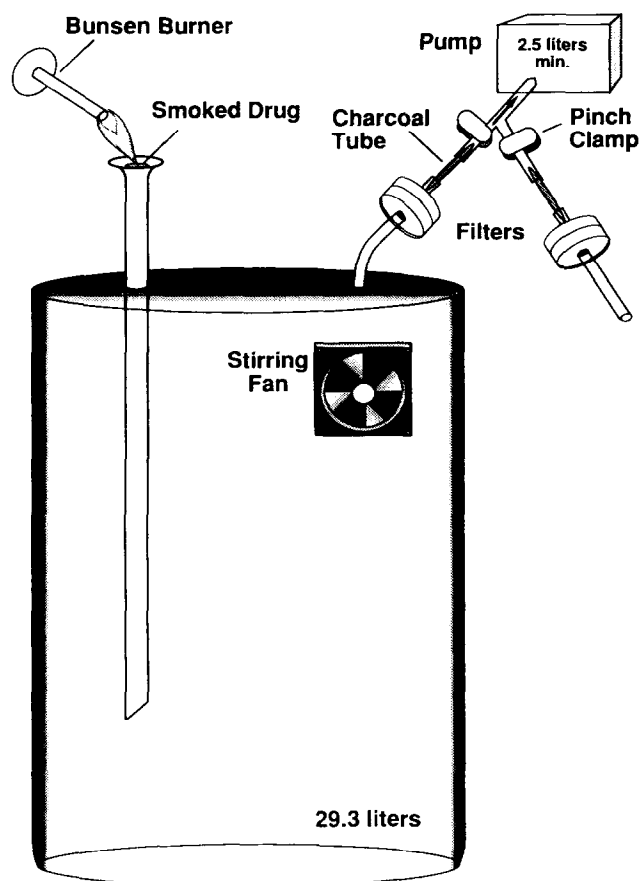


FIG. 3. A 29.3-l chamber used for disappearance studies. Drugs were introduced into the chamber using a Bunsen burner in conjunction with a pump. Filter cassettes and charcoal tubes were used to trap particles and vapor, respectively. Tubes and filters were changed while sampling proceeded through the other leg of the Y connector. A fan provided uniform distribution of the atmosphere within the chamber.

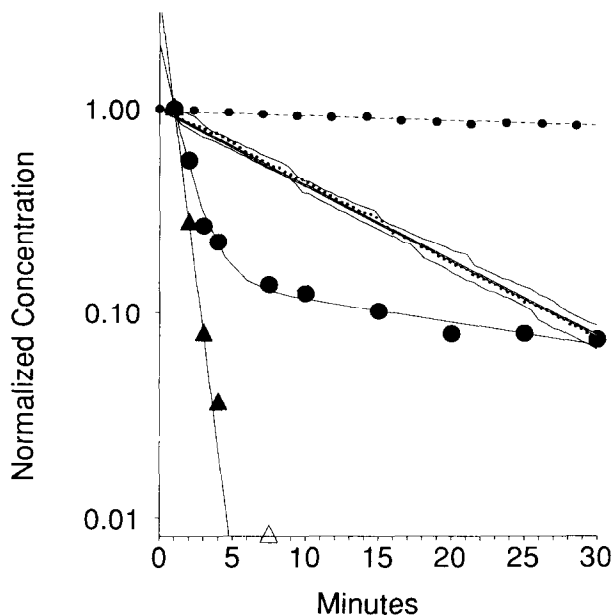


FIG. 4. Cocaine and MEG disappearance functions during high fan speeds. Cocaine (▲) disappeared rapidly as the particles impacted on the fan blades or chamber walls. Methylecgonidine (●) measured simultaneously with cocaine disappeared in two phases; MEG vapor alone (•) disappeared slowly, consistent with desorption from chamber walls. The double line is the theoretical disappearance for a single-compartment dilution model; ethanol (·), toluene (top solid line), and acetone (bottom solid line) closely followed this theoretical disappearance function. All observations were normalized to the initial observation. Δ , An outlier not included in the regression.

the MMAD for MEG particles vs. the cocaine MMAD's determined for the same sample (Fig. 7). These points were derived from 116 particle size determinations. The slope was virtually 1 with an intercept of 0. Observations with <1% MEG were highlighted with points. Computations were performed to determine the particle diameter given their proportion of the total mass, assuming the formation of separate particles for the two compounds. This is easily demonstrated to be the cube root of the product of the proportion of MEG present times the cubed diameter of the cocaine particle, assuming equal densities.

Vapor Pressure of Crack Constituents

Figure 8 presents the vapor pressure functions for MEG, benzoic acid, and cocaine based on selected observations from the literature, and on the values determined in this experiment. The vapor pressure constants for cocaine base and observations for benzoic acid have been published elsewhere (12,27) and are presented here for comparison. The regression function for cocaine was $\log P(\text{mm Hg}) = (-5884/T) + 13.02$. The benzoic acid regression function, derived from literature observations, was $\log P(\text{mm Hg}) = (-3590/T) + 9.80$.

Five observations on the vapor pressure of MEG have been published (4,15,29,31). The data of Clark et al. (4) (○, Fig. 8) did not fit with the observations of Zirkle (31), Matchett and Levine (15), and our four observations, and hence were omitted from the linear regression performed on these six points (●, Fig. 8). [Zirkle (31) reported two points, attributing one to Matchett and Levine (15); on examination of (15), we did not

find those data. These two points are labelled "Zirkle" in Fig. 8.] The function for MEG was $\log P(\text{mm Hg}) = (-3530/T) + 9.99$. An additional point was discovered in the literature (Δ , Fig. 8) (29) after the regression line was constructed, and it superimposed on the function.

Cocaine pyrolysis occurs around 170°C , a temperature adequate to raise its vapor pressure sufficiently to permit smoking, but < 1 mm Hg. As pyrolysis of cocaine occurs, the vapor pressure of the pyrolyzate is 2 or more orders of magnitude greater than that of cocaine base. As the aerosol cools, the vapor pressure of the cocaine drops more rapidly than that of MEG; cocaine droplet formation ensues first, along with the formation of a large droplet surface area on which MEG can condense subsequently.

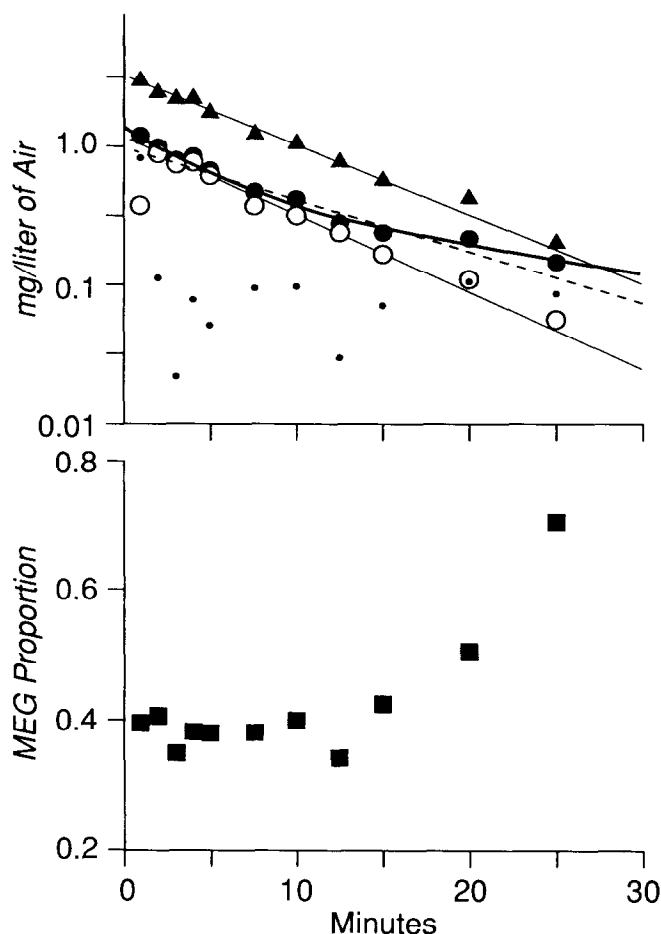


FIG. 5. Top: Cocaine and MEG disappearance functions at low fan speed. Cocaine (▲; $y = 3.341e^{-0.116x}$) disappeared only slightly more rapidly than predicted by a single compartment dilution model (dashed line; $y = 1e^{-0.085x}$). Total MEG (●) measured simultaneously with cocaine disappeared in two phases, with the slower component predominating in the last 15 min ($y = 1.022e^{-0.220x} + 0.416e^{-0.040x}$). MEG in the particulate phase on the filters (○) was relatively low during the 1st min of sampling, but increased in abundance and then disappeared in parallel with the drop in cocaine concentration ($y = 1.183e^{-0.127x}$). After the 1st min of condensation, MEG vapor concentrations (•) dropped by an order of magnitude. Bottom: As particles disappeared, the proportion of the atmosphere comprised by MEG increased (■).

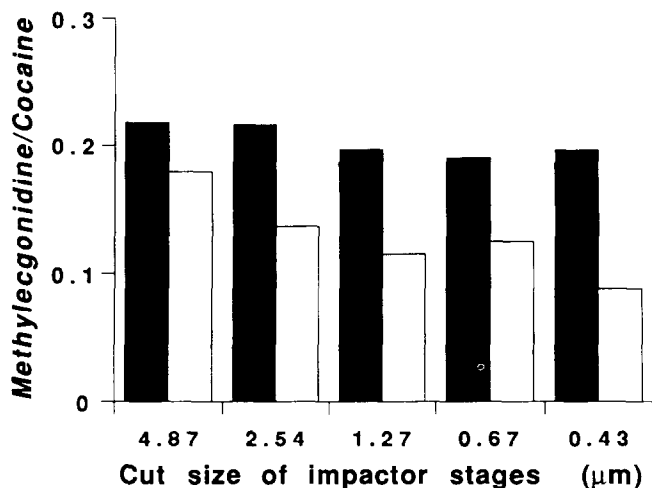


FIG. 6. Ratio of MEG to cocaine as a function of particle size and time of sampling. Conditions were similar to those of Fig. 5, except impactor samples were obtained at 2 (filled bars) and 15 min (open bars). MEG evaporated from the particles as they aged in the chamber. MEG as a proportion of total atmosphere increased (data not reported; as in Fig. 5), reflecting a greater proportion of MEG present in the vapor phase.

DISCUSSION

The physical characteristics of the atmosphere produced during the smoking of an alkaloidal drug is determined in a complex manner by the properties of the agent smoked and the techniques employed. There must be some difference between the temperature sufficient to develop a vapor pressure necessary for smoking, about 1 mm Hg, and that resulting in complete pyrolysis of the product. This temperature differential may be relatively small, because the volatilized agent is being drawn away from the flame as the drug is inhaled. As the vapor moves away from the heat source it cools, the vapor pressure drops, the atmosphere saturates, and the vapor begins to condense. In the case of crack smoking, the condensation occurs on the surface provided by "Bunsen" nuclei, the evanescent particles formed by an open flame. These condensation nuclei are responsible for the small size and monodisperse distribution observed with smoked drugs.

This study was undertaken in part to determine the vapor pressure of MEG, a pyrolysis product of cocaine, and to examine its relationship with cocaine droplets in the crack condensation aerosol. Methylecgonidine displays a vapor pressure function elevated above that for cocaine, and a more gradual decrease in vapor pressure as temperature decreases. Thus, cocaine condenses first, forming a viscous droplet. Methylecgonidine condenses at a lower temperature than cocaine, and the cocaine droplets provide the largest surface in close proximity as MEG begins to condense. Hence, MEG coats the crack droplet during the formation of the aerosol. It is unknown whether or to what extent MEG permeates or mixes with the cocaine base droplet.

As the crack atmosphere ages, evaporation can be demonstrated, as seen in this series of observations. The occurrence of evaporation implies that MEG may be present in the atmosphere, albeit at low levels, for a longer period of time than cocaine particles. Furthermore, because of its elevated vapor pressure, it may remain airborne in indoor environments long

after cocaine particles have impacted or impinged on indoor surfaces. Unlike cocaine, it is likely to be revolatilized with variation in indoor air temperature. This may have forensic as well as indoor air quality implications for nonsmokers residing in these environments.

In one experiment reported here, MEG condensation was not complete in the 1st min following volatilization of the cocaine and MEG paste. This may well be the result of the 25% pyrolysis product concentrations used here to ease the analytical challenge; these levels were as much as five to 10 times higher than that produced during crack smoking. The extent to which this partial condensation occurs during crack smoking is unclear, and would in any circumstance be determined in a complex manner by smoking technique. Were pyrolysis to occur, the absorption of MEG would share properties of both a gas and a particle. Furthermore, for condensation to occur, enough pyrolysis product must be present for saturation of the atmosphere at temperatures encountered between the flame and the sites of absorption in the respiratory tract. As the distance increases between the flame and the site of absorption, one would expect condensation to complete, and for reduction of MEG vapor concentration by wall absorption to commence. This would result in a tendency for MEG to migrate from the particle back into the vapor phase.

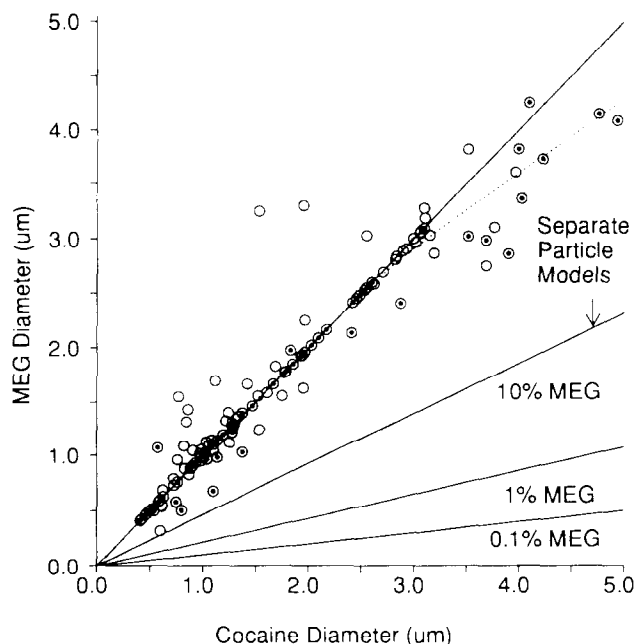


FIG. 7. Mass median aerodynamic diameter (MMAD) of MEG particles as a function of cocaine particle MMAD. The range of MEG proportion by weight was from 4.75–99.96%, $n = 116$. The slope of a robust regression (9) was indistinguishable from one with an intercept of zero; thus, the MEG and cocaine particles are the same diameter. The dashed line is a loess smoothing of the raw data (2). The other functions estimate the diameter of the MEG particle as if it were an independent particle existing as varying proportions of the total airborne mass concentration (i.e., the cube root of the product of the proportion of MEG present times the cubed diameter of the cocaine particle, assuming equal densities). The diameters of particles with < 1% MEG (○) superimpose principally on the unitary slope, not on or below the line representing the model for separate 1% MEG particles. Thus, MEG and cocaine form a single particle.

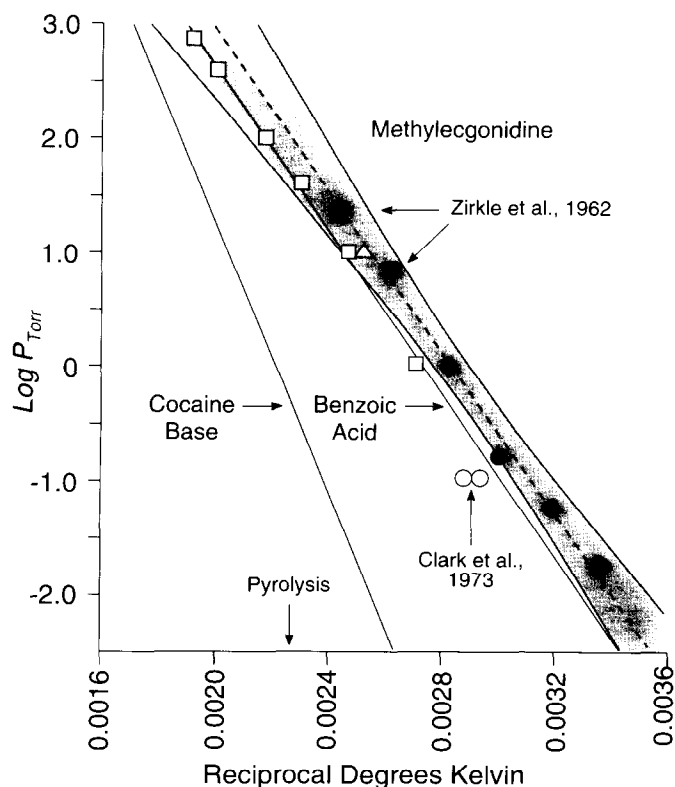


FIG. 8. The vapor pressure of cocaine, MEG (●), and benzoic acid (□) as a function of reciprocal degrees Kelvin. At temperatures where pyrolysis occurs ($>170^{\circ}\text{C}$), MEG has much a higher vapor pressure than cocaine. As temperatures cool, the vapor pressure of cocaine base drops more rapidly. The cocaine base vapor pressure function is $\log P(\text{mm Hg}) = (-5884/T) + 13.02$ (9); for benzoic acid: $\log P(\text{mm Hg}) = (-3590/T) + 9.80$ (27). The data of Clark et al. (2) were not included in the MEG regression, nor were the data of Zaugg (29) (Δ).

However, under typical crack-smoking conditions, the majority of the MEG delivered to the crack smoker is likely to be in the particulate phase, with a relatively constant airborne vapor concentration.

We also compared two techniques used to generate crack smoke for laboratory studies. We attached the smoke sources in series with an impactor and a vacuum source, "inhaling" at 5 l/min. The impactor inertially separates particles of different size by impacting them on collection surfaces. Cocaine and its pyrolysis products are deposited on different stages of the impactor as a function of their size. This technique might underestimate the total amount of pyrolysis by neglecting vapor, but this was not observed under the conditions examined. The size of the MEG and cocaine particles were the same, so we reported here on the whole particle. Because the amount of pyrolysis was usually $<1\%$, MEG could not have formed a separate aerosol, but coated the existing cocaine particles; if this were not the case, the ratio of particle diameters would have been about 4 : 1 under these conditions.

Both the hot-wire and crack pipe techniques pyrolyze cocaine. The hot-wire technique produces very large particles that are relatively few in number, and the size of the resultant particle increases with increasing mass of cocaine placed on the wire. This is unlike a torch and pipe, where the flame

produces many ($>10^8/\text{cc}$) "Bunsen" nuclei on which drug vapors condense, increasing the number and reducing the size of the resultant particles, and where the size of the particle is not dependent on the initial mass used. By providing NaCl nuclei, the hot-wire particle size was reduced.

We have developed a technique for estimating the alveolar deposition fraction of inhaled aerosols (1). These approximations reflect the restricted literature on aerosol deposition (a single nonhuman primate paper), and use a model developed within a more limited range of distribution variability than that encountered here. In the range of 1–4- μm particle diameters, the rat would display alveolar fractional deposition of <0.06 . The nose-breathing monkey and oral-breathing human would display a deposition fraction of approximately 0.3 with the particles observed here with a model crack pipe (MMAD: approximately 1 μm ; σ_g : 2.4). With the particles achieved with 30 mg using the hot-wire technique (MMAD: 4 μm ; σ_g : 3), the alveolar deposition fraction for human oral breathing would be approximately 0.44; however, a nose-breathing monkey would display only about 0.05 fractional deposition under these conditions. With a highly monodisperse small particle (MMAD: 1; σ_g : 1.3), such as we have achieved with a condensation aerosol generator (Wood, in preparation), the achieved deposition would be approximately 0.42 for the nose-breathing monkey and 0.3 for the human. The particle size produced by the hot wire alone is too large to achieve much lung deposition in obligate nasal-breathing rodents. One would expect the majority of the dose to impact in the nose of nasal obligate breathers such as the rat, or in the pharynx or at the bifurcation of the trachea during oral breathing (22). The aerosol generated by the typical crack pipe has an MMAD of $\leq 1 \mu\text{m}$, and thus would be readily deposited in the alveolar region of the human or nonhuman primate lung.

We estimated particle diameters using a Mercer cascade impactor, which is calibrated with latex beads traceable to the National Bureau of Standards. In studies of continuously generated cocaine atmospheres, MMAD's derived from Mercer impactor samples drawn from the undiluted stream agreed with measurements of the same atmosphere after dilution and size estimation with an optical particle size analyzer (HC15; Polytec GmbH, Waldbronn, Germany). The Casella impactor was designed to sample coarse aerosols (16) and was calibrated with polydisperse aerosols. The data analysis performed in Snyder et al. (23) was performed using the obsolete "stage factor" technique. The Mercer and other current impactors are calibrated in terms of the cutoff diameter (i.e., the aerodynamic diameter of a particle which is collected with 50% efficiency by a given stage). Mercer (17) demonstrated that less error is introduced with this technique than with stage factors. Numerical implementations of Marple's theory (13,20) predict performance of impactors well. We recalculated the cutoff diameters for the Casella impactor and found that the stage factors overestimate the MMAD. Recalculation of the data from Snyder et al. (not reported) resulted in estimates closer in size to those reported here, but still provided a larger value that we consider to be an overestimate. The general relationship between flow rate and particle size observed previously (23) was supported by the observations at higher flow rates reported here: a reduction in particle size with increasing flow rate. Furthermore, despite the use of the correction, the coarse four-stage resolution of the Casella impactor resulted in most of the mass being deposited on only the last two stages and the backup filter. This instrument yields an intrinsically less precise estimation of the particle size distribution than the Mercer impactor.

The hot-wire technique produces effects and blood levels that are related to the dose applied to the wire, despite the large MMAD of the particles. From these estimates, one can surmise that cocaine base can be administered to humans with low levels of pyrolyzate using the hot-wire technique, and the levels of alveolar deposition may be somewhat higher than that observed with crack pipes. The particle distribution is wide and extends into the submicron range; thus, a portion of the dose absorbed by a human inhaling from the wire is likely from the alveolar region. The large MMAD of the particle distribution produced by the hot-wire technique suggests significant deposition and absorption sites in the pharynx or at the tracheal bifurcation. If the hot-wire technique is used with obligate nose-breathers, or nose-breathing primates, a local dose delivered to tissues will differ from that obtained with a crack pipe: more upper airway deposition may occur, potentially altering the expression of toxicity in target tissues. This

also may result in a prolongation of the absorption of the inhaled drug. The addition of NaCl condensation nuclei reduced the diameter of the particles generated with the hot-wire technique, but not as effectively as the use of an open flame applied to cocaine base. The amount of pyrolyzate produced can be minimized by using smaller doses of cocaine base and higher inhalation rates; achieving repeatable amounts of pyrolyzates at higher concentrations may require other techniques.

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