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Formate in Urine as a Biological Indicator of Formaldehyde Exposure: A Review

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The presence of a small amount of endogenously derived formate in human urine is normal; however, formate derived from the metabolism of formaldehyde, several other industrial compounds and some pharmaceuticals may elevate the urine formate concentration above the normally expected values. This elevation in the urine formate concentration presents the possibility of using this as a tool for monitoring exposure to chemicals. Unfortunately, the use of urine formate as a technique for monitoring personal chemical exposure has yet to be evaluated. This review identifies several potentially important variables that could alter the extent to which formate is eliminated through the urine and that could affect the accuracy of using urine formate concentration as an indicator of chemical exposure. Some potentially important confounders that have been identified, but not evaluated adequately, include dietary intake, nutritional status and exposure to cigarette smoke. Furthermore, the metabolism and elimination kinetics have yet to be adequately demonstrated in humans. Without having controlled for potential confounders in previous pharmacokinetic studies, it is unknown whether or not the large range and variation observed in human studies is due to the confounders or to innate individual variability. Given the poor understanding of the normal variation of formate concentration in the urine, the use of it as a biological indicator of chemical exposure becomes questionnable. Without appreciable skin penetration, as in this case, the reliance upon air monitoring alone may be more practical. The evidence at this time suggests that the use of urine formate to monitor chemical exposure offers a broad opportunity for investigative research. At the present time, however, the interpretation of urine formate concentration in samples obtained from workers would be difficult.

Introduction

Formate, an endogenous product of single carbon (C_1) metabolism, is normally found in the urine of healthy individuals. Exposure to several common industrial compounds — such as formaldehyde, methanol and acetone — may contribute to increasing the amounts of formate in the body. It might be expected that any external exposure resulting in an elevation of the internal C_1 body load should lead to an increase in the rate of formate elimination. In practice, a simple predictable relationship between dose and elimination has not been demonstrated yet.

The analysis of biological media to determine the effect or extent of personal exposure to a substance is receiving increasing attention. To date, over 1000 substances reportedly have been determined in human biological media.[1] In theory, the application of biological monitoring offers benefits beyond the capabilities offered by environmental sampling.[2,3] First, the routes of exposure that contribute to the total body burden may be multiple and the amounts of exposure ambiguous. Therefore, a single short-term sample of a person's breathing zone air, for example, may poorly represent the actual total exposure. Furthermore, biological sampling may be related more closely to the extent of contaminant absorption. It may better reflect workload and individual uptake and it therefore may more closely parallel the personal hazard potential. Biological monitoring also can be used to assess the effectiveness of worker protective equipment. Finally, where cumulative body burden is of toxicologic consequence, the time integrated measurement of exposure — as determined in a biological sample — should be more meaningful than short-term environmental measurements. This is particularly advantageous when wide fluctuations in exposure concentration occur over a period of time.

To be useful for the practical application of assessing personal exposure, a biological monitoring procedure must meet certain requirements. Obviously, the analytical methods used should be accurate, precise, specific and as sensitive as possible. The procedure preferably should be non-invasive and should present minimal risk of injury. Overall, it should be inexpensive and easy to perform. Of equal importance is that the investigator know when to collect a sample or samples and whether to take any special precautions to prevent contamination or loss. To interpret the results, the investigator will require a knowledge of the normally expected median concentration and range for non-exposed individuals. If possible, potential confounding effects — such as diet, personal habits (*e.g.,* smoking and alcoholic beverage consumption), hobbies, age, sex, body weight, state of health, use of medications, and workload — should be taken into account. The above factors may influence directly the intrapersonal, and especially the interpersonal, variability of the results within the normal range. One can best understand these interdependent factors through the study and understanding of the metabolism, excretory pathways and pharmacokinetics of the compound of interest.

This communication attempts to review the literature and provide a perspective on the many biological and exogenous

factors that may influence the concentration of formate in urine. On a broader scope, anyone interested in evaluating any potential biological exposure indicator should be benefited by considering these factors.

Sources of Formate and Its Elimination

Formate, as the sodium salt ($HCOO \cdot Na$), is one of the simplest endogenous forms of carbon in man and is the intermediate in many anabolic and catabolic reactions. Formate or formaldehyde has been shown to be involved in single carbon transfers from many essential amino acids — including glycine, histidine, tryptophan and serine — and in the synthesis of purines, pyrimidines, methionine and choline.[4-7] The tetrahydrofolic acid (THF) pathway is the primary means through which the above metabolism occurs. Once formate has entered into the one-carbon unit pool, numerous reactions can occur that direct formate to various other pathways — including the citric acid pathway where it can be utilized for energy needs, releasing carbon dioxide (CO_2) and water.[8,9] In addition to the major THF pathway, there is evidence that formate may be converted to CO_2 and water by reactions with peroxide[10] or catalase.[11-13] This overall scheme for the role of formate *in vivo* is displayed in Figure 1.

Since formate can arise from many sources, there always appears to be a certain amount of it in the blood. Excess formate that is not utilized metabolically will be eliminated in the urine.[14] Formate concentrations reported in the urine of non-exposed individuals are summarized in Table I. The average urine formate concentration in non-exposed individuals, as reported in literature during the past two decades, ranges from 11.7 to 18 mg/L. The upper range is only 35% greater than the lowest reported average concentration. There was, however, a considerably larger range of individual differences among subjects within each study. The larger inter-individual differences might reflect the complexity and multiplicity of the factors involved in formate metabolism.

Studies have been undertaken that address the metabolic fate of formate in rats by the use of radiolabeled chemical precursors of formate, such as C^{14} formaldehyde.[15-18] No studies, however, have been found that involve higher primates. The monkey and dog are considered to be much more comparable animal models of the human elimination of formaldehyde and formate than is the rat; therefore, these animals should be the species of choice for metabolic studies.[19]

Chemical Precursors to Endogenous Formate

In addition to worker exposure to formic acid aerosol, there are several compounds and pharmaceuticals that can be transformed metabolically into formate. Formate precursor compounds that may be encountered in industry include formaldehyde, methanol, halomethanes and acetone.[20-29] Drugs that owe their activity to the release of formaldehyde or are deactivated metabolically through demethylation reactions include methenamine, N-methyltriazines, hexamethyl-melamine, N-isopropyl-methoxamine, ephedrine, and methylephedrine.[30-33] Certain pectin-rich fruits contain considerable amounts of esterified methanol that may be liberated in the digestive tract and absorbed.[34] Some studies have reported a correlation between methanol exposure and urine formate concentration while others have not.[22-24,35-37]

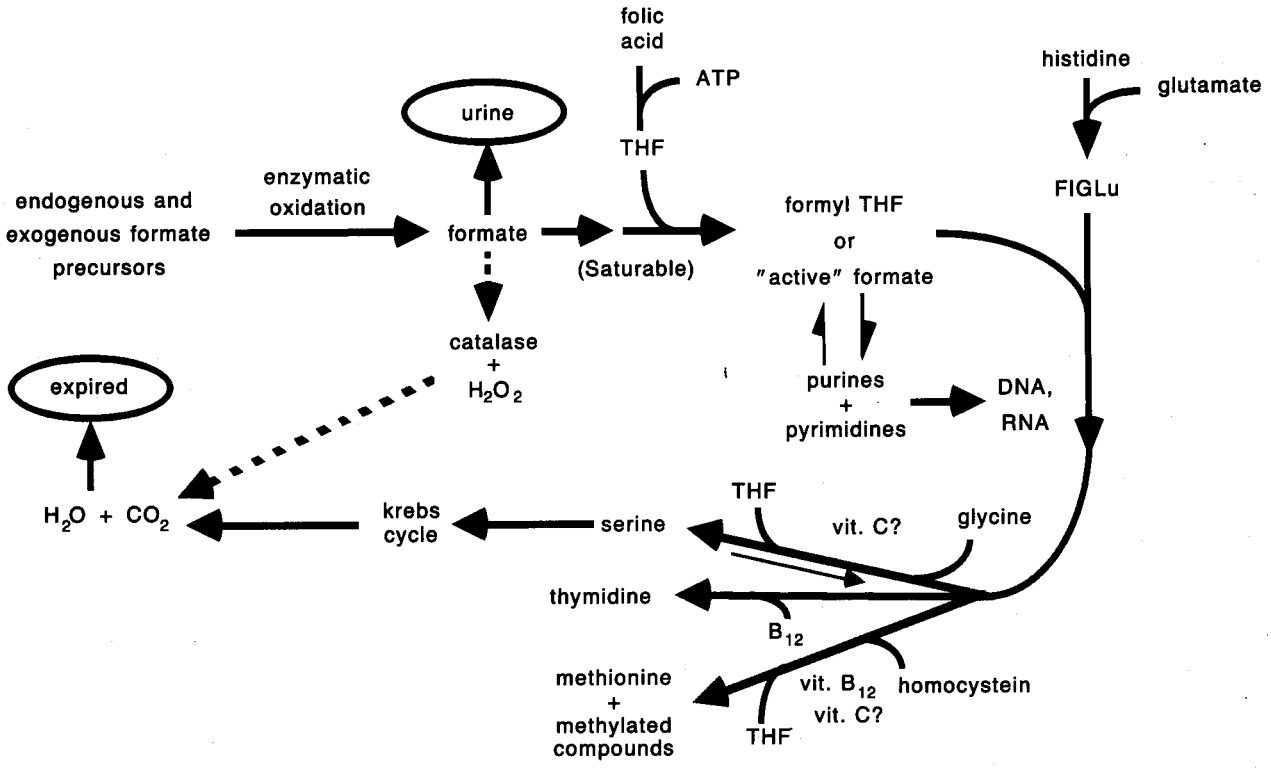

Figure 1 — Simplified metabolic pathways involving formate.

TABLE I
Reported Normal Concentration of Formate or Formic Acid in Human Urine[A]

Mean (mg/L ± SD)	Range (mg/L)	Number of Participants	Method	Reference
12.5	0.6-31.9 (105 samples)	35	GC analysis of methyl formate	50
13 ± 6.4	2-30	20	Enzymatic	80
11.9 ± 6.4	1-25	15	GC analysis CO (methane)	36
11.7 ± 5.6 (afternoon)	4-22	15	GC analysis CO (methane)	36
13.1 ± 3.9	-	20	GC analysis CO (methane)	36
17.1 ± 4.1 (9.4 ± 3.5 mg/g creatinine)	-	17	Enzymatic	80
18 ± 28	0-129	30	GC analysis of CO (methane)	79
13 ± 1.7	6.8-30.3	12	Chromotropic acid analysis of formaldehyde	48
60	30-120	12	Mercuric chloride precipitation	51

[A]In many of the references cited no information is given concerning the collection program of the urine specimens. Frequently, it also is not stated how many samples per individual were obtained. In addition, no information is provided that considers dietary, alcoholic beverage or other influences on formate concentration.

Formaldehyde

The literature is extensive concerning the metabolic pathways for formaldehyde in animals. At least two pathways concerning the metabolism of formaldehyde to formate, shown in Figure 1, have been identified. One enzyme, termed formaldehyde dehydrogenase (FDH), is involved specifically with the oxidation of formaldehyde and has been identified in human liver and erythrocytes.[38-40] The enzyme also has been determined tentatively to be present in relatively high concentrations in rat nasal cavities.[41] FDH is involved in the release of formate by cleavage of the thiol ester with glutathione (GSH).[38,39,42] *In vitro* studies with human tissue also have shown that nonspecific but functionally related aldehyde dehydrogenase and catalase, which are not dependent on GSH, are both capable of converting formaldehyde to formate.[38]

In vitro experiments with human blood showed that formaldehyde is quickly oxidized to formate after its transport into erythrocytes.[40] Since formaldehyde can be handled so effectively by not only the liver but by the blood as well, the rapid disappearance of formaldehyde from the blood can be understood. In one study, research using monkeys that were given a rapid intravenous administration of formaldehyde resulted in a reported plasma half-life of approximately 1.5 min.[43] During the disappearance of formaldehyde, a corresponding rapid increase in the plasma levels of formate was observed.[43]

More recent research indicates that while high plasma concentrations of formaldehyde are removed rapidly, a trace baseline concentration frequently, or nearly always, exists.[44] An average of 2.24 μg and 2.61 μg formaldehyde per gram of venous blood was reported in unexposed rats and humans, respectively. When human volunteers were exposed to 1.9 ppm of formaldehyde for a period of 40 min, the blood concentration was not elevated significantly.[44] These baseline concentrations and the rate-kinetics for formaldehyde's removal suggest that formaldehyde is replenished constantly by *in vivo* processes, but that the removal process is capable of maintaining plasma concentrations in equilibrium at low concentrations. In the above study, urine or plasma formate concentrations were not measured and it is not known from this study if urine formate concentrations were elevated after inhalation of formaldehyde. The high variation in blood formaldehyde concentration observed within the human volunteers and lack of response to exposure, however, would discourage the use of blood samples for measuring formaldehyde exposure.

Formaldehyde does not appear to be removed *in vivo* by protein binding since it was not found to form covalent adducts at sites distant from the nasal mucosa.[18] The lack of covalent adduct formation is not surprising given the normal presence of endogenous formaldehyde;[44] instead, internal formaldehyde is anabolized.[45]

The preceding discussion should not suggest that formaldehyde does not form covalent adducts at the site of exposure in epithelial cells. Covalent binding with proteins of the nasal mucosa has been found ot increase in a linear manner with increasing airborne concentration.[46] Similarly, topical applications of formaldehyde appear to bind irreversibly, primarily with epithelial tissue proteins; this allows for only 5% or less of the administered dose to be absorbed internally.[47-49]

Distribution studies in which rats were used have found that inhalation of radiolabeled formaldehyde is followed by elimination in expired air (approximately 40%), urine (17%), feces (5%), with the remainder being deposited in tissues (35%).[18] Since formaldehyde is a precursor for a large number of biological compounds, the radioactivity remaining in the tissues is believed to be related to metabolic incorporation. Evidence has been provided that indicates that formaldehyde is converted to formate prior to incorporation through one-carbon metabolism.[18] The loss of this incorporated formate occurs slowly over a period of several days. The mechanism of this loss, possibly occurring through oxidation to carbon monoxide or by elimination in the urine as formate, is not known.

The literature describes several field studies that have attempted to investigate the effect of formaldehyde exposure upon urine formate concentration. In one investigation, the exposures of twelve medical students working in an anatomy laboratory and four industrial workers were studied by Einbrodt *et al.*,[50] who sought to explore that relationship. Formaldehyde exposure to the students lasted for 3 hr with concentrations ranging from 0.26 to 0.92 ppm (mean 0.51 ppm). Urine obtained from all 12 students at the end of the exposure period was pooled into one sample. Urine collected during the 21 hr after exposure was pooled into a second sample. The urine formaldehyde concentration was found to be higher in the post-exposure period (2.5 mg/L) than immediately after exposure (1.0 mg/L). Formic acid concentrations in the urine collected in the post-exposure period were also higher (52 ± 20 mg/L) than immediately after exposure (35 + 11 mg/L). These differences were statistically different using a t-test ($p \leq 0.05$).

It is unclear why the authors of the above study did not collect a baseline sample before exposure rather than immediately after 3 hr of exposure to formaldehyde. If a pre-exposure urine formate concentration had been established for each individual and compared to the post-exposure formate concentration from samples collected over an extended period of time, perhaps the difference would have been more pronounced.

In the same study, urine samples also were collected from four factory workers exposed to an average of 1 ppm (1.28 mg/m^3) of formaldehyde. During the day of exposure, a 24-hr urine sample was collected from each worker; this collection was repeated for each worker after 6 days of no exposure to formaldehyde. From this study it was reported that on the day of exposure the average urine formic acid concentration was 152 mg/L, while 6 days later the average concentration was 24 mg/L. This difference is statistically significant ($p < 0.01$).

In the above study, the students and workers inhaled approximately 2.5 and 13 mg of formaldehyde, respectively during exposure, while their respective urine formic acid concentrations were 52 mg/L and 151.7 mg/L. Even if a baseline urine formate concentration of 24 mg/L is subtracted from the results, the magnitude of the elimination of formate compared to the measured air exposure is not validated by conventional mass-balance relationships. If one assumes a baseline formic acid concentration of up to 24 mg/L and a urine volume of 1 L/day, the students excreted approximately 7.5 M of formic acid for every mole of exposure to formaldehyde. The formate excretion mass for workers was approximately 8 times higher than their exposure. While this anomaly was not considered by the original authors, perhaps the excess elimination could be explained by concomitant dermal penetration of formaldehyde, the possibility that personal exposure was greater than the general room air concentrations, or that other chemical exposures that could be eliminated as formic acid were also present. In a separate laboratory study in which sodium formate was given orally to human volunteers, only 2.1% of the administered dose was eliminated as formate in the urine within 24 hr.[51] This inconsistency between laboratory and field dose-elimination results needs further study.

Gottschling[52,53] monitored 35 anatomy lab students who were exposed to formaldehyde during the dissection of animals preserved in formalin. The students' exposures to formaldehyde lasted only 2 hr, once a week, for three weeks. Average personal exposures measured during each of the three weekly exposures were only 0.107, 0.111 and 0.036 ppm. The highest single air exposure concentration was 0.36 ppm. The students reportedly wore gloves during dissection. A urine sample was collected from each participant in the morning before class and again anytime within 2 hr after class. No attempt was made to obtain information on possible confounding influences.

The urinalysis results demonstrated a wide interpersonal and intrapersonal range and variation in the morning formate concentration as found in the three weekly samples. Only one-third of the students had a baseline average urine formate concentration that varied by less than 5 mg formate/L over the three weeks tested. Although mean post exposure formate concentrations were slightly higher for all three weeks, none were significantly higher.

Gottschling[53] considered adjusting the urine formate concentration by normalizing to a standard urine parameter. The pre- and post-exposure specific gravity of the urine was compared and found not to differ significantly. It was assumed that since the baseline urine formate concentration fluctuated significantly over time, correcting for specific gravity would not reduce baseline fluctuations or the post exposure results. None of the other studies attempted to adjust the urine data for dilution (*i.e.*, using specific gravity or creatinine).

Dietary and Personal Factors Affecting Formate Elimination

Diet and Nutritional Status

Diet and nutritional status are perhaps the most influential factors to the level of formate in the urine and could account for the broad individual day-to-day fluctuations. Unfortunately, only fragmentary information on this relationship has been reported.

High intakes of carbohydrate or protein rich food are believed to increase formate output through the urine.[54] In addition, some foods and beverages have been reported to contain small amounts of formaldehyde. For instance, formaldehyde has been determined to exist in meat and poultry (0.5 to 6 mg/kg), in fish (6 to 14 mg/kg), in fruits (apples and pears, 2 to 8 mg/kg), and in smoked meats (3 to 30 mg/kg).[55] Formaldehyde also has been reported in popular soft drinks at a concentration of approximately 8 mg/kg as well as in beer (range 0.1 to 1.5 mg/kg).[56] Whether formaldehyde exists in a free state in foods and beverages or possibly is created during the analytical determination of unstable precursor compounds is not certain.

Formic acid occurs naturally in animals and in most plants. The formic acid content reported for some common foods and beverages is as follows: fruits, 20 to 40 mg/kg; honey, 20 to 2000 mg/kg; wines, 1 to 340 mg/kg; roasted coffee, 30 to 40 mg/kg; evaporated milk, 30 to 40 mg/kg; and cheese, 20 to 200 mg/kg.[57] Formic acid is added intentionally to some foods such as baked goods, ice cream, soft drinks and fruit drinks as a flavor adjunct.[57] Dietary consumption in most adults has been estimated to be between 0.4 to 1.2 mg of formic acid per day.[57] Occupational exposure to formic acid in the air in many industries also may occur.[58]

Ethyl formate is found to occur naturally in many fruits and alcoholic beverages, and it is sometimes added as a food flavoring.[57] Ethyl formate is known to be unstable in water and to decompose.[59] While no specific reference was found in the literature regarding the metabolism of ethyl formate, a formaldehyde-like end product most probably occurs.[60] Average daily intake for ethyl formate has been estimated to be between 48 and 84 mg per day; ethyl formate exists in fruits, alcoholic beverages and as a food flavoring.[57]

The ethanol found in alcoholic beverages may elevate the serum formate concentration after consumption. This effect is believed to be due strictly to ethanol's inhibitory influence on the tetrahydrofolate pathway in humans.[61] Investigative studies of ethanol's influence on urine formate concentration have not been found in the literature.

Nutritional status may be an important variable in influencing urine formate concentration. A deficiency in any of the essential biochemical components in the tetrahydrofolic acid pathway (as identified in Figure 1) will reduce the proportion of serum formate metabolized to CO_2 and water. Animal studies have shown that nutritional deficiencies in folic acid and vitamin B_{12} result in an accumulation of formic acid in the blood and elevated excretion of formate in the urine.[62-66] This imbalance can be corrected by dietary supplementation resulting in a return to a lower urine formate concentration.[19,67,68]

Cigarette Smoke

Formaldehyde can be found in cigarette smoke. An individual smoking one pack of cigarettes per day would inhale approximately 0.82 mg of formaldehyde.[69] This is below a worker's daily intake of 9.7 mg of formaldehyde if the worker is exposed to 1 ppm in the workplace air for 8 hr.[70] Cigarette smoke, however, contains additional compounds that may be metabolized to formate.[71] An evaluation of the effect of cigarette smoking on urine formate concentration is needed.

The Elimination Kinetics of Formate and Derivatives

The rate of biotransformation of industrial compounds to formate, and the elimination of formate, are understood only marginally. Excess formate that is not utilized metabolically will be at least partly eliminated in the urine (Figure 1). If the metabolic pathway is saturable, then it should be possible to demonstrate a proportional increase in elimination of formate in the urine with equal unit increases in dose.

The above theoretical relationship may be more complex, however, as indicated by the results of one experiment.[51] In that experiment, two large doses, consisting of 1 and 2 g of formic acid, were given orally to human volunteers. The percentages of the doses eliminated in the urine were 2.1% and 3.3%, respectively. Although the amount of dose eliminated is indeed different and therefore dose dependent, the two data points are insufficient to determine the shape of a dose-elimination relationship. Clearly, additional experimental data are needed at dose levels below 1 g.

Whereas formaldehyde has a very short residence time in plasma (*i.e.*, $t_{1/2}$ = 1.5 min), the half-live for circulating formate is 30 min or longer. Figure 2 presents plasma half-life data from an experiment with a monkey that was infused intravenously with several concentrations of sodium formate.[72] The results indicate that the plasma half-life for formate appears dose-related, at least at high dose levels, but shows signs of becoming constant at lower dose levels. Similar low dose levels could be experienced during workplace exposure.

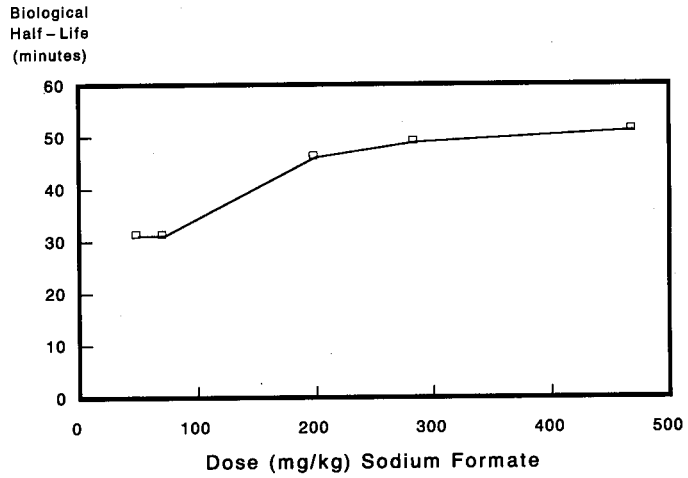

Figure 2 — Dose related biological half-life for sodium formate in the monkey. Data from Reference 72.

Elimination kinetic data on formate in man have been reported in two studies. In one study, the average plasma half-life in 11 volunteers that were given an intravenous, unspecified dose of formate, was 55 min.[9,19] Another study reported that the plasma half-life was 45 min when 3 g of formate was given orally to one individual, while in a second individual, the plasma half-life was 46 min after 4.4 g of sodium formate was taken.[51]

In this same study, 11 volunteers were given a 1-g and a 2-g oral dose of formate on two occasions and urine samples were collected for the periods 0 to 6 hr, 6 to 12 hr, and 12 to 24 hr.[51] It was found, under the conditions of this study, that after the two doses were given the output of formic acid in urine over the 24-hr collection period was 1.9 times and 5.6 times greater than normal, respectively. The increased amount of eliminated formate in the urine, however, represented only 2.2% and 3.3% of the formic acid dose, leaving the remainder unaccounted for. Elimination was rapid. In each dosing regimen, 80% and 90% of the increased elimination occurred within 6 hr of the administration. This study indicates that large bolus doses of formate result in large, rapid increases in the urine concentration. A much smaller elevation in the baseline formic acid concentration, however, was seen when the smaller dose was administered, suggesting that workplace exposures may not be adequate to detect a noticeable increase in urine. These data represent the only finding reported in the literature regarding a laboratory study of the concentration of formate or formic acid in the urine after a known dose of a compound was administered.

Discussion

In spite of the many potential confounding influences on formate elimination that could add to the variability of urine formate concentration, Einbrodt reported a statistically significant elevation in two groups of exposed individuals after moderate exposure to formaldehyde.[50] Gottschling also reported a slight elevation in urine formate, although not statistically significant, after exposure to minimal amounts of formaldehyde.[52,53] Each investigation involved different schedules for sampling and different methods of sampling and analysis of the air and urine. Each investigation also reported substantial personal and interpersonal variation of urine formate concentrations, both before and after exposure. For those interested in using biological samples procedures, however, there is encouragement in the above two studies that suggest urine formate may be elevated after exposure to formaldehyde. Unfortunately, the urine collection methodologies of both field investigations were deficient in addressing many of the variables identified in this review and there are considerable uncertainties regarding the accuracy of the reported exposures.

The influence of diet and nutritional status barely has been explored. The rate of formate disappearance from the blood of folate deficient monkeys is almost twice that of control monkeys on a normal diet.[62] Presumably, folate deficiency may be widespread as a consequence of the typical American diet.[73-77] Folate deficiency could be monitored in human participants by measuring urine 5-N-formininoglutamate (FIGlu).[78-80] The concentrations of formate and FIGlu in folic acid and vitamin B_{12} deficient rats are related directly.[10,67,81]

It has been assumed that the morning pre-exposure urine formate concentration can be used as a control urine sample and compared to postworkshift urine samples. In Gottschling's study, however, which compared the morning and afternoon formate concentration in 35 non-exposed persons, the correlation coefficient was only 0.24.[52] If such wide variation normally occurs in intraday elimination, it may be advantageous to collect time integrated samples rather than place full weight on a single pre- or post-exposure void. Furthermore, the wide variation in baseline formate excretion may preclude the use of urine formate as an indicator of individual exposure. A more valid use of urine formate as an indicator of chemical exposure may be to use group data averages. If such is the case, minimal sample size should be determined.

Biological monitoring has been suggested as especially useful where skin absorption might occur and the adverse action of exposure may be systemic. The utility of biological monitoring often is enhanced further when the dose is cumulative and the biological measurement can reveal exposures that have occurred over a period exceeding one day. The literature suggests that elevated formate concentration in urine is a short-term outcome of exposure. The metabolic utilization of excess formate, however, is poorly understood and a portion of the excess formate, or a related entity, may be temporarily accumulated and eliminated gradually.

Formate itself is a relatively innocuous metabolic product that can result from exposure to a more toxic and reactive precursor compound. One might expect that in the specific case of formaldehyde, where its carcinogenic and irritating activity possibly involves direct, localized, covalent binding with DNA or proteins, measured urine formate levels would not reflect specific *in vivo* damage.

Recently, favorable results from an attempt to correlate urinary formic acid concentrations with exposure to formic acid in air were reported.[23] Assuming a linear relation exists between exposure and urine concentration, the above report indicates that an exposure of greater than 3.5 μg formic acid/L in air is required to elevate the urine formic acid concentration above baseline (about 15 mg/g creatinine). A recently reported field evaluation demonstrates the proposition that urinary formate concentrations do not correlate well with low formaldehyde air concentrations.[82] In that study, personal time-weighted average exposures did not exceed 0.6 ppm (0.7 μg/L) and, as expected, no detectable elevation in urinary formate concentration was seen.

The practical use of any new technique must be preceded by well designed experimental studies that would provide the knowledge to allow the user the ability to derive accurate and meaningful conclusions from the data. Some of the gaps in the authors' present understanding of this topic have been identified in this paper as a contribution to this effort.

In conclusion, the measurement of formate in urine may offer the user a new tool for better assessing worker exposure to formaldehyde and possibly to several other chemical compounds. Unfortunately, because formate is naturally excreted and nonspecific to any single chemical exposure, the existence of many unresolved influences upon the results would make interpretation difficult. Additional pharmacokinetic studies are needed that take into account the effects of diet, smoking and nutritional status before an adequate determination of the utility of urine formate tests can be made.

Recommendations

Investigations into the primary cause of wide daily and interday fluctuations in urine formate concentration need to be performed. Influences — such as fluid balance, consumption of protein, starch and ethanol — should be considered. Normalizing formate concentration by time and urine volume and correcting by creatinine concentration or specific gravity should be explored.

Controlled laboratory investigations are needed to improve the understanding of the elimination of formate in persons exposed to relevant concentrations of chemicals that could be metabolized to formate. It needs to be established whether the elimination rate, and eliminated proportion, of absorbed dose is dose-dependent over the exposure concentration range found in the workplace. It is not clear from this review whether small amounts of excess formate is eliminated rapidly after exposure or over an extended period of time.

Additional field studies are needed using persons exposed to formaldehyde (and possibly other formate precursor compounds) at air concentrations at and below the compound's allowable standard for periods of time equal to the entire workshift. It should be useful if each investigation could consider, by use of factorial analysis, as many variables as possible and evaluate the impact of each variable on the results.

Finally, future investigations should select one of the many improved analytical methods for air and urine analysis that are now available. Although a review of the analytical methods reported in the literature to measure formate was outside the intended scope of this paper, a comprehensive review and comparison of the methods would be necessary before selecting a single analytical procedure for routine use.

This review has discussed biological factors that might influence the urinary excretion of formate. These factors should be kept in mind when referring to previously reported field study results or if plans are being made to explore the use of formate as an indicator of workplace exposure.

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