REVIEW ARTICLE

DISORDERS OF FLUIDS AND ELECTROLYTES

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Integration of Acid–Base and Electrolyte Disorders

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THIS REVIEW DESCRIBES A METHOD OF ANALYZING ACID–BASE DISORDERS that incorporates insights from the traditional, bicarbonate-centered model and the Stewart (or strong ion) model (Table 1).[1-6] Acid–base balance and electrolyte homeostasis are intricately connected at the cellular level and in clinical disorders. This article emphasizes the integration of the principles of mass balance and electroneutrality — which are prominently featured in the strong ion model (also known as the physicochemical model) — for interpretation of acid–base phenomena. Most acid–base abnormalities can be diagnosed and interpreted with the use of the traditional approach. Why, then, should the strong ion theory be incorporated into teaching about acid–base balance? Although the Stewart model is not primarily a mathematical expression of a confirmed reality, it is relevant because it is a powerful construct that can shed light on an important biologic system.

Included in this article are several case vignettes that show the explanatory power of the strong ion approach in clinical practice. Some of these examples have been presented in a companion article on the physiological approach to acid–base balance by Berend et al.[7] Other cases that are interpreted with a strong ion approach are included in the Supplementary Appendix, available with the full text of this article at NEJM.org. The more complex chemistry of the hydrogen-ion concentration in intracellular and extracellular fluid compartments is beyond the scope of this article.

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N Engl J Med 2014;371:1821-31.
DOI: 10.1056/NEJMra1215672

BICARBONATE-CENTERED AND STRONG ION APPROACHES

The traditional model uses easily measured concentrations of blood carbon dioxide [CO_2] and bicarbonate [HCO_3^-].[6] It is the basis of the Henderson–Hasselbalch equation:

$$pH = pK + \log_{10}\left(\frac{[HCO_3^-]}{0.03\ (PaCO_2)}\right), \quad (1)$$

where pK is the acid dissociation constant, $PaCO_2$ the partial pressure of arterial carbon dioxide, and 0.03 the solubility of CO_2 in blood.

The overall equilibrium between carbon dioxide and bicarbonate is shown below:

$$CO_2 + H_2O \longleftrightarrow H_2CO_3 \longleftrightarrow H^+ + HCO_3^-, \quad (2)$$

where H_2CO_3 denotes carbonic acid, and H^+ hydrogen.

In a teaching model, this relationship shows how alterations in the partial pressure of carbon dioxide (PCO_2) or levels of hydrogen or bicarbonate affect the other variables through mass balance. The fact that the hydrogen ion concentra-

Table 1. Comparison of the Key Elements Associated with Two Models of Acid–Base Balance.*

Traditional Approach Based on Bicarbonate–Carbon Dioxide	Physicochemical (Stewart) Approach†
CO_2/HCO_3^- equilibrium: $CO_2 + H_2O \longleftrightarrow H_2CO_3 \longleftrightarrow H^+ + HCO_3^-$ and for $[CO_3^{-2}]$ $2[HCO_3^-] \longleftrightarrow [CO_3^{-2}] + [H_2O]$	CO_2/HCO_3^- equilibrium: $CO_2 + H_2O \longleftrightarrow H_2CO_3 \longleftrightarrow H^+ + HCO_3^-$ and for $[CO_3^{-2}]$ $2[HCO_3^-] \longleftrightarrow [CO_3^{-2}] + [H_2O] + [CO_2]$
Henderson–Hasselbalch equation: $pH = pK + \log_{10}\left(\frac{[HCO_3^-]}{0.03\ (Paco_2)}\right)$	Water dissociation: $K_w = \frac{[H^+][OH^-]}{H_2O}$ Weak acid (HA) dissociation: $[H^+]\ [A^-] = K_A\ [HA]$; weak acid conservation: $[A_{tot}] = [HA] + [A^-]$
Anion gap = $[Na^+] - ([Cl^-] + [HCO_3^-])$ mmol per liter	Strong ion difference (mmol per liter) = $[Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - [Cl^-]$; [strong ion difference] $- [A^-] = [HCO_3^-] + [CO_3^{-2}] + [(OH^-)] - [H^+]$; or, strong ion difference $- [A^-] \approx [HCO_3^-]$
Delta/delta = $\frac{(\text{anion gap} - 12)}{(25 - [HCO_3^-])}$	
Example of expected compensation: $Pco_2 = 1.5\ [HCO_3^-] + 8 \pm 2$ The Winters formula for respiratory compensation of metabolic acidosis, in which Pco_2 is dependent on the decrease in bicarbonate	Example of expected compensation: $Pco_2 = 1.5\ [HCO_3^-] + 8 \pm 2$ The Winters formula for respiratory compensation of metabolic acidosis, in which Pco_2 is dependent on the decrease in bicarbonate

* The traditional approach is based on bicarbonate–carbon dioxide. The physicochemical (Stewart) approach is dependent on the strong ion difference and A_{tot}, the total content of albumin, phosphate, and circulating nonvolatile weak acids and their dissociated anions. H_2CO_3 denotes carbonic acid, and $PaCO_2$ partial pressure of arterial carbon dioxide.

† Relationships featuring electroneutrality are emphasized in the Stewart model. The equation for strong ion difference $- [A^-]$ can be reduced to approximately $[HCO_3^-]$ because $[HCO_3^-]$ is much greater than $[H^+]$, $[OH^-]$, and $[CO_3^{-2}]$. Stewart's equation (not shown), based on the relationships above, has been mathematically reduced to the Henderson–Hasselbalch equation (bicarbonate/CO_2 method).[2]

tion is more than a million times lower than the bicarbonate level indicates that other forces are at work in the regulation of pH.

As in any chemical reaction in equilibrium, a change in the concentration of the reactant or product will move the reaction in the direction that would reestablish equilibrium (Le Châtelier's principle). If this principle is applied to equation 2, metabolic acidosis may be attributed to either the addition of hydrogen, with the consumption of bicarbonate as the reaction shifts to the left, or the removal of bicarbonate from the body, resulting in increased hydrogen as the reaction shifts to the right (from carbon dioxide) to replace lost bicarbonate. The observed relation between arterial Pco_2 ($PaCO_2$) and bicarbonate effectively predicts the direction but not the magnitude or time course of respiratory and renal compensations. Only empirical observations can determine the appropriate degree of compensation.

The anion gap, consisting of the sum total of all unmeasured charged species (predominantly albumin) in plasma, is calculated below as

$$\text{anion gap} = [Na^+] - ([Cl^-] + [HCO_3^-]). \quad (3)$$

The anion gap is used in the differential diagnosis of metabolic acidosis.[8-10] It can suggest a cause for unmeasured anions. Possible causes include lactic acidosis, ketoacidosis, and uremic acidosis; ingestion of salicylate, methanol, ethylene glycol, or propylene glycol; and many inborn errors of metabolism. It is assumed that the unmeasured anion is added as the protonated acid (such as lactic acid). However, a severe form of metabolic acidosis results from treatment with sodium thiosulfate, a compound that has no hydrogen.[11]

In contrast to the anion gap shown in equation 3 above, the physicochemical model emphasizes that all cation and anion concentrations must balance, according to the laws of electroneutrality.[3] The independent balance of each ion,

when disrupted, provides a mechanism for the acid–base condition. In their classic article, Peters and Van Slyke defined acid–base balance in the blood as the chemical state resulting from the balance between cations and anions.[12] Carrying this idea to the extreme, one could view metabolic acid–base disorders as the predicted consequences of primary fluid and electrolyte imbalance.

Strong ions such as sodium and chloride are assumed to be completely dissociated in body water but can be lost or gained disproportionately. When the sum of all negatively charged ions (predominantly chloride) is subtracted from the sum of all positively charged strong ions, a value known as the strong ion difference (in millimoles per liter) is introduced. The strong ion difference is calculated as shown below:

$$\text{strong ion difference} = [Na^+]+[K^+]+[Ca^{2+}]+[Mg^{2+}]-[Cl^-], \quad (4)$$

where Ca^{2+} denotes calcium, and Mg^{2+} magnesium.

As shown in equation 5 below, the total content of albumin, phosphate, and circulating nonvolatile weak acids [HA] and their dissociated anions [A^-] is referred to as [A_{tot}] in the Stewart model:

$$[A_{tot}]=[HA]+[A^-]. \quad (5)$$

As shown in equation 6 below, in which CO_3^{-2} denotes carbonate and OH^- hydroxide, an expression for remaining charged species, considered to be the dependent variables, is

$$[\text{strong ion difference}]-[A^-] = [HCO_3^-]+[CO_3^{-2}]+[(OH^-)]-[H^+], \quad (6)$$

in which the levels of carbonate, hydroxide, and hydrogen are much lower than the levels of bicarbonate. Any developed difference in the ionic charge, or strong ion difference, determines the bicarbonate concentration. Essential to this argument is that any difference in an unbalanced charge will immediately result in the appearance or disappearance of bicarbonate formed from ubiquitous and neutral carbon dioxide and water. It is also expected that the changes in the bicarbonate concentration will begin to occur at a very minimal strong ion difference, since large charge separations are not possible. We can assume that electrostatic forces come into play until changes in bicarbonate concentrations match the charge separations among other ionic species. Clearly, electroneutrality in the macroenvironment always exists.

One drawback of using equation 6 in a clinical calculation of the hydrogen concentration is that the error in measurements of electrolytes in the millimolar range cannot allow for an accurate determination of the hydrogen level in nanomolar concentrations.

As shown in Table 1, the Stewart (or physicochemical) model of acid–base balance is quantitatively based on the view that the hydrogen and bicarbonate concentrations are not independently determined. Instead, they are dependent on the following: carbon dioxide ($PaCO_2$) and its spontaneous relationship with hydrogen and bicarbonate, the dissociation of water (the abundant source of hydrogen within body fluids), the dissolved strong ions, the strong ion difference, and A_{tot}, which is the sum of all buffer pairs (mostly weak acids) that move toward equilibrium with a dissociated anion [A^-] according to the dissociation constant for each (e.g., albumin with its net negative charge under physiological conditions).[13]

In keeping with the laws of electroneutrality, all charged species must balance. This requires that any change in the concentration of one of the charged variables (the strong ion difference) must be matched by a change in the concentration of another charged species. According to constraints in this internal system, the hydrogen and bicarbonate concentrations are dependent on the other variables, the total mass of which is conserved.

The simultaneous mathematical solution of these reactions is complex and is not required to diagnose acid–base disorders. Furthermore, both experimental and clinical observations can be explained with the use of either model. Yet the physicochemical model is useful in revealing individual processes in the development of an acid–base disturbance because it associates the abnormality with specific electrolyte disturbances. The traditional model uses the calculated, and useful, anion gap to elucidate the pathophysiology of metabolic disorders. The usual calculation for the

Table 2. Acid–Base Disorders and Their Causes According to the Relationship between Gains and Losses of Circulating Cations or Anions.*

Metabolic alkalosis
Decrease (loss) of anion
Hypochloremic
Gastrointestinal
Vomiting
Chloridorrhea (villous adenoma, some chloride secretory diarrheas)
Renal
Chloruretic agents (loop diuretics, thiazides)
Chloride channelopathies (e.g., the Bartter syndrome, the Gitelman syndrome)
Hypokalemia leading to loss of chloride
Sweat
Cystic fibrosis
Hypoalbuminemic state[13]: malnutrition
Increase (gain) of cation
Sodium citrate, sodium lactate, sodium bicarbonate, sodium acetate
Hypernatremic
Hyperaldosteronism
Hypercalcemic
Milk alkali syndrome, calcium carbonate
Metabolic acidosis
Increase (gain) of anion
Hyperchloremic (potassium chloride, calcium chloride, hydrogen chloride, sodium chloride, arginine hydrochloride, lysine hydrochloride, ammonium chloride)
Anion-gap acidosis
Lactic acidosis
Diabetic ketoacidosis
Other unmeasured anions
Thiosulfate
Hyperphosphatemic
Decrease (loss) of cation (sodium and potassium)
Renal
Renal tubular acidosis
Natriuretic agents (e.g., amiloride, triamterene)
Sodium with anions in urine: ketoacids, D-lactate, hippurate
Hypoaldosteronism
Gastrointestinal
Diarrhea with bicarbonate or bacterial organic anions in stool
Vomiting pancreatic secretions

* All metabolic acid–base disorders can be viewed in the context of the relative losses or gains of cations or anions in body fluids. Hypophosphatemia is not listed because the plasma phosphate level is normally low.

anion gap is shown in equation 3. For this equality to hold true, for electroneutrality purposes, the anion gap must be the net value for a complex mixture of all ionic species not included in the calculation, such as albumin, other proteins, calcium, magnesium, potassium, and phosphate, plus any additional anions such as lactate or acetoacetate. To illustrate the usefulness of a more inclusive approach in separating out various components of the anion gap, an anion gap hypothetically could be calculated as simply $[Na^+]-[HCO_3^-]$. From a charge point of view, it works out, but obviously, hyperchloremic acidosis could not be distinguished from an "anion gap" acidosis.

The anion-gap equation could be rearranged to solve for the bicarbonate concentration instead of unmeasured anions:

$$[Na^+]-([Cl^-]+[AG])=[HCO_3^-],$$

where AG denotes the anion gap.

This is analogous to the strong ion difference. The anion gap, which is usually calculated with the use of plasma bicarbonate, is useful clinically. If every charged species were known and measured, the equation could be rearranged to calculate the bicarbonate concentration, but often the unmeasured ion is unknown. How, then, does the strong ion difference increase or decrease? The answer lies in specific gains or losses of electrolytes such as sodium and chloride in a different proportion to each other than the proportion in the normal extracellular fluid. The first step in understanding how an acid–base disorder develops is to know or assume the specific electrolyte content of any gained fluids (e.g., intravenous fluids) or lost fluids (e.g., gastrointestinal fluids, sweat, or urinary fluids).

Since the normal concentration ratio of sodium to chloride in extracellular fluid is approximately 140:100, an increase in the sodium level, a decrease in the chloride level, or both will increase the strong ion difference and the bicarbonate concentration will increase (metabolic alkalosis), according to electroneutrality requirements.[3] When the strong ion difference decreases, pH and the bicarbonate level will decrease (metabolic acidosis). The electroneutrality relationship in equation 6 can be useful in diagnosing the causes of metabolic alkalosis and metabolic acidosis shown in Table 2.

METABOLIC DISTURBANCES AND STRONG IONS

Acid–base balance is dependent on strong ions in the macroscopic sense because the same cellular mechanisms regulate acid–base homeostasis and electrolyte homeostasis. The following case vignette illustrates this point:

> A 31-year-old woman with gastroenteritis had been vomiting for 2 days. She was weak and hypotensive. Laboratory tests revealed a sodium concentration of 125 mmol per liter, potassium 2.6 mmol per liter, chloride 72 mmol per liter, and bicarbonate 40 mmol per liter. The arterial pH was 7.54, the $Paco_2$ 48 mm Hg, and the urinary pH 5.0.

Depletion of the extracellular fluid from vomiting creates profound needs to conserve sodium and water and preserve potassium balance; these mechanisms are clearly obstacles to maintaining a normal blood pH and bicarbonate concentration. With volume and potassium depletion, metabolic alkalosis is maintained, not corrected, by the kidneys.[14,15] Low extracellular fluid volume and low blood pressure increase angiotensin II and aldosterone levels. Increased sodium reabsorption through proximal tubular sodium–hydrogen exchange and the collecting-duct sodium channel, accompanied by hydrogen secretion by the hydrogen ATPase and the potassium–hydrogen ATPase, in turn increases bicarbonate reabsorption until the urinary pH decreases as it becomes free of bicarbonate. This paradoxical aciduria in the midst of alkalemia is evidence that blood pH depends on strong ion balance. The alkalemia will be corrected only with sufficient replacement of sodium, chloride, and potassium. In this patient, after the administration of 0.9% normal saline with potassium chloride, the electrolyte status improved, and the urinary pH increased to 8.0 with the prompt excretion of sodium, potassium, and bicarbonate. In this clinical situation, the interdependency of acid–base and electrolyte balance is self-evident. If this were not the case, and kidney function instead focused on maintaining a normal acid–base balance, the bicarbonate generated by vomiting would result in the urinary loss of even larger quantities of sodium, potassium, and water, leading to life-threatening volume and potassium depletion.

The traditional acid–base approach tacitly overlaps with aspects of the strong ion theory (Table 1). Consider the familiar concept known as the "delta-delta" (Δ-Δ), the increase (Δ) in the anion gap versus the decrease (Δ) in the bicarbonate level.[8,9]

All metabolic acid–base disorders are associated with either a change in the concentration of sodium, potassium, calcium, chloride, hydrogen phosphate, or albumin or a change in the anion gap. The normal anion gap can be adjusted for hypoalbuminemia by allowing for 2.5 mmol per liter of negative charge for each 1 g per deciliter of albumin concentration.[13] The relative change in the bicarbonate level and the anion gap (Δ-Δ) is only part of the electroneutrality requirement. The net sum of all cation and anion electrolyte charge gaps must cancel out. In the search for a "Δ-Δ-Δ-Δ-Δ-Δ," clues about any acid–base disorder will emerge.

A finding of an increase in the anion gap above the normal concentration (the Δ anion gap) that exceeds the decrease in the bicarbonate concentration (Δ bicarbonate) may indicate mixed metabolic acidosis and metabolic alkalosis. The following case shows that a ratio other than 1:1 is not pathognomonic for a mixed acid–base disturbance:

> Before a cardiac arrest, a 67-year-old man with an acute myocardial infarction had normal levels of serum electrolytes (level of sodium 140 mmol per liter, potassium 4.0 mmol per liter, chloride 103 mmol per liter, and bicarbonate 25 mmol per liter). While he was anuric after the cardiac arrest, his laboratory tests showed a sodium level of 140 mmol per liter, potassium 5.0 mmol per liter, chloride 62 mmol per liter, and bicarbonate 5 mmol per liter. The arterial pH was 7.10, and the $Paco_2$ was 16 mm Hg. The lactate level was 60 mmol per liter, and the anion gap was 73 mmol per liter.

This patient had severe anion-gap metabolic acidosis due to lactate overproduction from tissue hypoperfusion. Since lactate production can result in blood lactate concentrations greater than a normal bicarbonate concentration, what

happens when the bicarbonate concentration decreases almost to zero? Hydrogen might be preferentially reactive with other tissue buffer systems, but a decrease in the chloride level is often observed, yielding a hypochloremic anion-gap acidosis.[16,17] With lactate acting as a strong ion, the strong ion difference $[Na^+]-[Cl^-]-[lactate^-]$ is decreased and the bicarbonate concentration decreases to achieve electroneutrality. Chloride moves into cells, probably in exchange for lactate or bicarbonate. In this case, there was no clinical evidence of superimposed metabolic alkalosis:

$$\Delta\,[HCO_3^-]+\Delta\,[Cl^-]=\Delta\,[AG]=[\text{lactate}].$$

Also, consider examples of metabolic alkalosis in which the increase in a strong cation is balanced by an increase in the bicarbonate concentration, as in the following case, which was also described by Berend et al.[7]:

> A 50-year-old woman with a recent onset of hypertension had the following laboratory results: sodium level 150 mmol per liter, potassium 2.2 mmol per liter, chloride 103 mmol per liter, and bicarbonate 32 mmol per liter. The arterial pH was 7.50, and the $Paco_2$ was 43 mm Hg. She was found to have an aldosterone-secreting adrenal adenoma.

In this case, the change in the bicarbonate level was associated with an increased sodium concentration, which is often seen in primary hyperaldosteronism and is attributable to increased function of epithelial sodium channels in renal cortical collecting-duct principal cells. Mild hypernatremia probably occurred as a result of extracellular fluid expansion that decreased vasopressin release, with a consequent decrease in renal reabsorption of water. The plasma chloride level was not increased in proportion to the sodium level, which is consistent with less chloride than sodium retention in primary hyperaldosteronism.[18] Loss of chloride, a feature of "aldosterone escape from edema," is linked to decreased sodium–chloride cotransport in the distal renal tubule.[19] Hypokalemia in turn is associated with increased loss of urinary chloride. Thus,

$$\Delta\,[HCO_3^-]=\Delta\,[Na^+]+\Delta\,[K^+]-\Delta\,[Cl^-],$$

with changes in each of these strong ions contributing to the alkalosis.

Treatment of the alkalosis in this patient with hyperaldosteronism will require replacement with potassium chloride. Administering chloride in the form of saline would worsen the hypokalemia, and administering potassium without chloride would not correct it; thus, the term "saline unresponsive" is more accurate than "chloride unresponsive" as a description of this type of alkalosis.

Hypercalcemia will increase the strong ion difference and is associated with metabolic alkalosis.[20] The milk alkali syndrome, which is often caused by excessive ingestion of calcium-containing antacids, is characterized by alkalosis and hypercalcemia. In contrast, hypercalcemia in primary hyperparathyroidism is associated with a proximal renal tubular metabolic acidosis rather than metabolic alkalosis. This observation may be explained by the decrease in the strong ion difference due to losses of urinary sodium resulting from inhibition of proximal tubular sodium–hydrogen exchange by parathyroid hormone.[21]

GASTROINTESTINAL LOSSES OF STRONG IONS

Losses of ions due to diarrhea are associated with the development of metabolic acidosis[22] or metabolic alkalosis. Since depletion of extracellular volume can occur in cases of acidosis or alkalosis and may be initiated by losses of sodium and chloride in any ratio, the term "contraction alkalosis" is a misnomer. As shown in the following case, the relative content of the strong ions lost (sodium and potassium vs. chloride),[23] not the site of the loss, determines the acid–base disorder:

> A 40-year-old woman who underwent a colonic resection for ulcerative colitis had excessive liquid drainage from an ileostomy. Her laboratory results revealed a plasma sodium level of 138 mmol per liter, potassium 5.0 mmol per liter, chloride 110 mmol per liter, and bicarbonate 15 mmol per liter. The arterial pH was 7.30, and the $Paco_2$ was 32 mm Hg.

In this case, the loss of watery small-intestinal and pancreatic secretions, which have high sodi-

um and bicarbonate levels and very low chloride levels, would result in the relative retention of more chloride than sodium in the extracellular fluid, causing hyperchloremic acidosis. In cases of colonic diarrhea, hyperchloremic acidosis may develop because of loss of sodium and potassium with organic anions of bacterial origin, such as acetate, rather than bicarbonate per se.[23]

When diarrhea is the cause of metabolic alkalosis, rather than acidosis, the mechanism is determined by measuring the electrolyte content in stool. Large losses of chloride may occur in patients who have villous adenomas or other secretory diarrheas that cause depletion of chloride, as shown in the following case, described by Berend et al.[7]:

> Large volumes of watery diarrhea from infectious gastroenteritis developed in a 22-year-old man. Laboratory tests revealed a plasma sodium concentration of 140 mmol per liter, potassium 3.0 mmol per liter, chloride 86 mmol per liter, and bicarbonate 38 mmol per liter. The arterial pH was 7.60, and the $Paco_2$ was 40 mm Hg.

In this case, the electrolyte concentrations in liquid stool, if measured, would probably show a charge gap, in which $(Na^+ + K^+) - Cl^-$ would be less than the normal plasma bicarbonate concentration. High losses of chloride in stool, like losses of chloride from vomiting or after the use of loop diuretics, cause hypochloremic alkalosis.

URINARY CHARGE GAP AND STRONG IONS

Measurements of urinary electrolyte concentrations and flow rate indicate renal acid–base function even without measurement of urinary bicarbonate. As shown in equation 7, the urinary net charge compares the loss of measured strong cations (sodium and potassium) with the loss of chloride[24]:

$$\text{Urinary net charge gap} = [U_{Na}^+] + [U_K^+] - [U_{Cl}^-]. \quad (7)$$

NEGATIVE URINARY CHARGE GAP

A negative value for the urinary net charge gap indicates the presence of the unmeasured cation, ammonium (excretion of ammonium chloride). The loss of ammonium chloride in the urine of a patient with metabolic acidosis is an appropriate compensation, since the very process of excreting acid in this way has an alkalinizing effect on body fluids. The loss of net acid in the form of ammonium chloride is a normal renal response to nonrenal causes of metabolic acidosis, such as severe watery diarrhea. The losses of urinary chloride result in an increased plasma strong ion difference, which in turn permits the formation of more bicarbonate.

However, in a patient with metabolic alkalosis, a relative excess of chloride in the urine strongly suggests that the losses of urinary chloride cause the metabolic alkalosis by increasing the plasma strong ion difference. In the following case, such losses of urinary chloride led to hypochloremic alkalosis:

> An 80-year-old man with congestive heart failure received furosemide until all peripheral edema disappeared. Laboratory tests revealed a sodium level of 130 mmol per liter, potassium 2.5 mmol per liter, chloride 80 mmol per liter, and bicarbonate 40 mmol per liter. The arterial pH was 7.50, and the $Paco_2$ was 53 mm Hg.

In this patient, the sodium–potassium–chloride cotransporter was inhibited by furosemide (in the thick ascending limb of the loop of Henle). Under these circumstances, the stoichiometric balance of sodium, potassium, and chloride was 1:1:2, and proportionately more chloride than sodium was lost in the urine. Thus, there is a direct explanation for the hypochloremic metabolic alkalosis in this patient. Inhibition of the sodium–chloride cotransporter of the distal tubule by thiazides (stoichiometric balance between sodium and chloride, 1:1) is also predictive of metabolic alkalosis because of the greater loss of chloride than sodium from the extracellular fluid. In addition to chloride-wasting diuretics, many hereditary disorders of sodium and chloride transport by the renal tubules (so-called channelopathies) may cause acid–base disorders, as shown in Table 2.

POSITIVE URINARY CHARGE GAP

A positive value for the urinary net charge gap indicates excretion of an unmeasured anion. The lost, unmeasured anion may be bicarbonate or nonbicarbonate anions such as ketones, lactate, L-lactate, D-lactate, and hippurate in persons who sniff glue. Such loss of anions will decrease

the plasma strong ion difference and acidify the extracellular fluid as the process returns chloride to the circulation.[10,25] If the urinary clearance of these nonchloride anions is high enough that they do not accumulate as a plasma anion gap, then the hyperchloremia may be mistaken for renal tubular acidosis.[24] Without those nonbicarbonate anions, metabolic acidosis with the loss of urinary sodium and potassium and retention of chloride (the positive-charge gap) will result in a decreased plasma strong ion difference, constituting a renal cause of acidosis (e.g., carbonic anhydrase inhibition or renal tubular acidosis).

If metabolic alkalosis is present, a positive urinary gap suggests that the renal loss of strong cations (sodium and potassium) and conservation of chloride will acidify the extracellular fluid because of a decrease in the plasma strong ion difference and in the bicarbonate concentration.

The excretion patterns of urinary electrolytes reflect the ability of the kidney to counteract nonrenal acid–base disorders. The capacity of the kidney to excrete ammonium chloride in acidosis allows for elimination of anions with conservation of sodium for volume and potassium for potassium balance. This potassium-sparing effect of urinary ammonium is evident in hypokalemic stimulation of ammoniagenesis.

The traditional physiological approach interprets the urine electrolytes to deduce the presence of ammonium and bicarbonate with less emphasis on the strong ion pathogenesis of acid–base disorders. The physicochemical model emphasizes the relative losses of the actual measured quantities to determine the cause of the disturbance. Both perspectives are enlightening.

COMPENSATION FOR RESPIRATORY DISORDERS AND URINARY STRONG IONS

The ratio of bicarbonate to $Paco_2$ in the Henderson–Hasselbalch equation (equation 1) is a simple way to illustrate the initial disturbance and then the modulating effect of the compensatory response on pH. In respiratory conditions, the $Paco_2$ is the initial abnormality leading to sharp, sudden changes in pH, with little change in strong ion concentrations. Over time, however, the change in the level of chloride and reciprocal changes in the level of bicarbonate are the major factors that allow pH to return toward normal values. The hyperchloremic renal compensation for respiratory alkalosis is the excretion of filtered sodium and potassium with bicarbonate, because low $Paco_2$ decreases proximal and distal hydrogen secretion. As the plasma strong ion difference decreases, the plasma bicarbonate concentration will decrease.

In respiratory acidosis, high $Paco_2$ increases production of ammonia by the kidney, and the excretion of ammonium chloride with a negative urinary net charge, shown in equation 7, results in hypochloremia, an increased plasma strong ion difference, and an elevated plasma bicarbonate concentration. The elevated $Paco_2$ increases the renal reabsorption of sodium and bicarbonate, so the compensation is maintained. If the $Paco_2$ is abruptly lowered by means of a ventilator, the compensatory response transitions to posthypercapnic hypochloremic metabolic alkalosis, which will not resolve until the chloride that is lost as ammonium chloride is replenished.

Figure 1 (facing page). Renal Tubular Cells with Transporters That Are Targets of Hormones, Diuretics, and Mutations Affecting Acid–Base Balance.

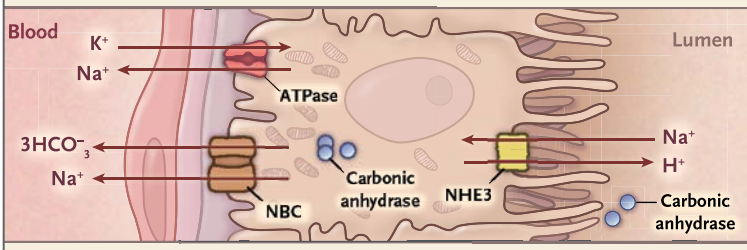
Similar transporters in the gastrointestinal tract that are associated with disease are not shown. All cell transporters on the blood side interface with interstitial fluid (not shown) before transport into blood. AE1 denotes anion exchanger 1, ENaC epithelial sodium channel, NBC sodium bicarbonate cotransporter, NCC sodium chloride cotransporter, NHE3 sodium–hydrogen exchange, and NKCC sodium–potassium 2-chloride cotransporter.

INTRAVENOUS FLUIDS AND CONTENT OF STRONG IONS

The gain of fluids containing strong ions in ratios dissimilar to those in the extracellular fluid also affects acid–base balance, as shown in the following case, which was also described by Berend et al.[7] in their article about the physiological approach:

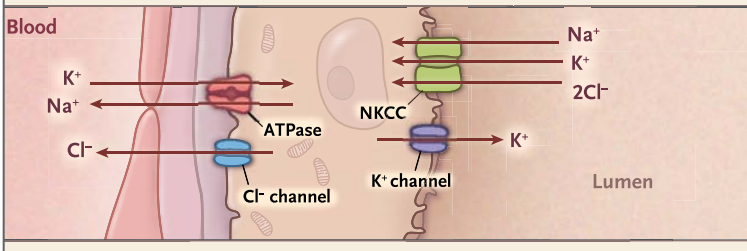
> A 22-year-old woman who had been injured in an accident received 6 liters of isotonic saline, after which the level of sodium was 135 mmol per liter, potassium 3.8 mmol per liter, chloride 115 mmol per liter, and bicarbonate 18 mmol per liter. The arterial pH was 7.28, and the $Paco_2$ was 39 mm Hg. The urinary sodium level was 65 mmol

A Proximal tubular cell



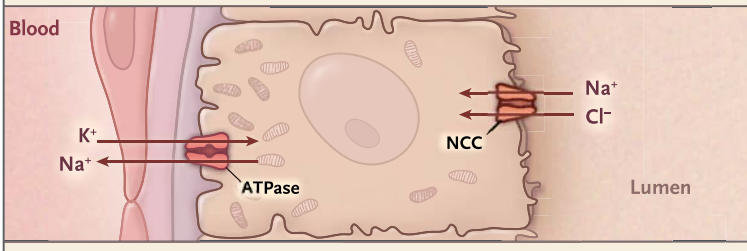
The stoichiometric balance of three HCO_3^- ions per one Na^+ ion is $3HCO_3^-$. Disorders of Na^+–H^+ exchange (NHE3), Na^+, $3HCO_3^-$ (NBC), and carbonic anhydrase cause proximal renal tubular acidosis.

B Thick ascending limb cell of the loop of Henle



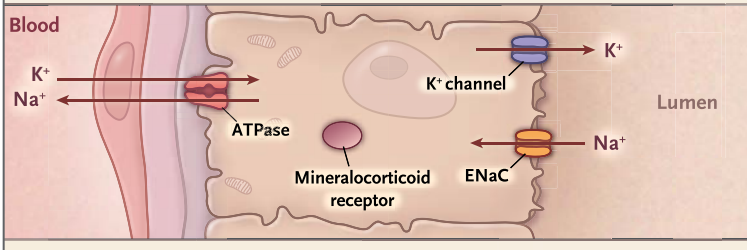
Mutations in NKCC, K^+, or the Cl^- channels cause the Bartter syndrome, with hypokalemic, hypochloremic metabolic alkalosis and extracellular fluid volume depletion. This syndrome can also be caused by the use of furosemide and NKCC inhibition.

C Cortical distal tubular cell



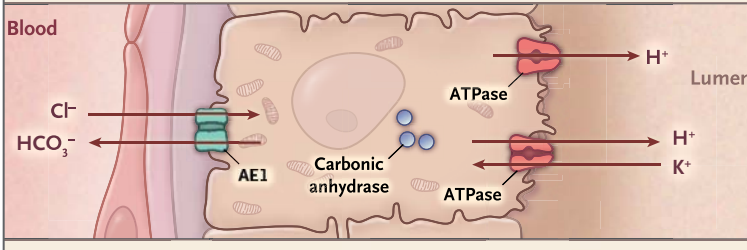
Inhibition of NaCl cotransport (NCC) by thiazide or an inactivating mutation in Gitelman's syndrome causes hypochloremic, hypokalemic metabolic alkalosis, whereas increased function, pseudohypoaldosteronism type 2, results in hyperkalemic metabolic acidosis.

D Principal cell, cortical collecting duct



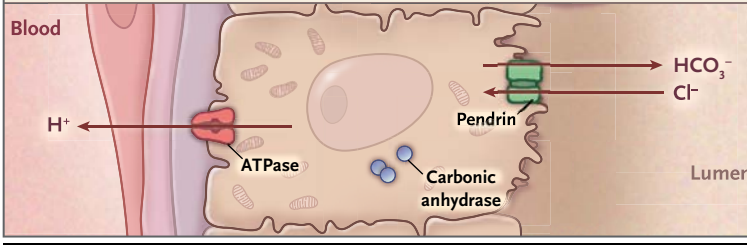
Increased ENaC, the luminal Na^+ channel (Liddle's syndrome), and hyperaldosteronism cause hypertension and hypokalemic metabolic alkalosis. Decreased ENaC, mineralocorticoid-receptor blockade, and hypoaldosteronism cause hypovolemia and hyperkalemic metabolic acidosis.

E Type A (acid-secreting) intercalated cell, cortical collecting duct



The type A cell mutations of luminal H^+–ATPase subunits and mutations in AE1 with decreased Cl^-–HCO_3^- activity cause distal renal tubular acidosis. K^+–H^+ ATPase in type A cells couples H^+ secretion with K^+ reabsorption.

F Type B (HCO_3^--secreting) intercalated cell, cortical collecting duct



Decreased function of the type B cell Cl^-–HCO_3^- exchanger, pendrin, is a cause of chloride-wasting metabolic alkalosis.

per liter, potassium 15 mmol per liter, and chloride 110 mmol per liter.

This is an example of saline-induced acidosis,[26] which develops because the infusion of a proportionately high sodium chloride–containing solution, one with a sodium-to-chloride ratio of less than 140:100, will decrease the plasma strong ion difference and the bicarbonate concentration. The insufficient urinary excretion of the extra chloride as ammonium chloride leads to metabolic acidosis. The infusion of saline with its 1:1 sodium-to-chloride ratio, resulting in hyperchloremic acidosis, is the converse of inhibition of the 1:1 sodium-to-chloride transport ratio in thiazide-induced diuresis and hypochloremic metabolic alkalosis.

Even Ringer's lactate, with a level of sodium of 130 mmol per liter, chloride 109 mmol per liter, and lactate 28 mmol per liter, can cause hyperchloremic acidosis because the ratio of sodium to chloride is smaller than the ratio of sodium to chloride in the normal extracellular fluid.[26,27] Thus, what matters is the content and amount of infused fluids.

CONCLUSIONS

Clinical evidence can be interpreted with the use of both the strong ion theory and the traditional bicarbonate-centered approach to provide an optimal understanding of acid–base disorders. Electrolyte concentrations of plasma may be altered by the gains and losses associated with intravenous fluids and with urinary, intestinal, or sweat-gland secretions. An understanding of the consequences of these disturbances helps in the diagnosis and treatment of the associated acid–base disorders.

The evidence connecting acid–base balance with electrolyte balance is apparent at the cellular level (i.e., ion transporters, their stoichiometric balance, and the hormones that regulate them) (Fig. 1) and in clinical practice. The fact that transporters often couple a strong ion such as sodium or potassium with hydrogen, or chloride with bicarbonate,[28-30] suggests an ultimate coherence between the two approaches (Fig. 1). As more is learned about the molecular nature of disorders of epithelial-cell transport as well as about intracellular pH, it will become more important to understand interactions between carbon dioxide and bicarbonate with strong ions and cellular buffers in the body.[31]

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Integration of Acid–Base and Electrolyte Disorders

TO THE EDITOR: In his review on acid–base disorders, Seifter (Nov. 6 issue)[1] attempts to integrate the "traditional, bicarbonate-centered model" described by Davenport[2] and Boron[3] with Stewart's strong-ion-difference model[4]:

$$\text{strong ion difference (in mmol per liter)} = [Na^+] + [K+] + [Ca^{2+}] + [Mg^{2+}] - [Cl^-].$$

In unbuffered salt solutions,

$$\text{strong ion difference} = [OH^-] - [H^+]$$

and is thus a pH surrogate. However, adding buffers as strong ion salts (e.g., sodium bicarbonate equilibrated with carbon dioxide, or sodium lactate equilibrated with lactic acid) increases the strong ion difference while having variable or even no effects on pH. Thus the strong ion difference does not uniquely define pH. Changes in the strong ion difference are a consequence of adding acids or bases as strong ion salts; they do not cause pH to change. Stewart[4] makes the fundamental error of mistaking correlation for causation. Proteins are generally sensitive to pH per se, not the strong ion difference. No biologic mechanisms exist for directly sensing or regulating the strong ion difference in cells, blood, or other compartments (e.g., the cerebrospinal fluid) — domains where pH is both sensed and regulated. Seifter advocates the strong ion difference as a diagnostic tool, rather like the anion gap. Although this analysis may indirectly provide information on acid–base control, the strong ion difference offers no new mechanistic insight because it does not have a causal role in pH changes.

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DOI: 10.1056/NEJMc1414731

TO THE EDITOR: Seifter's "integration" of the bicarbonate-centered and strong ion approaches to acid–base disorders has added a new layer of confusion and leads to incorrect conclusions. As examples, neither hypoalbuminemia nor hypernatremia causes metabolic alkalosis. These are facts, not opinions. The problems of the strong ion approach have been elucidated in detail by us and others.[1,2] The fundamental problem is that the strong ion approach is anchored exclusively in the chemistry of solutions in a beaker, where strong ions, weak acids, and carbon dioxide determine the bicarbonate concentration and pH. In the body, however, a system of cellular processes and transporters regulates acid–base homeostasis (as described in Seifter's article), so that dependent and independent events cannot be isolated. These physiological events are fully considered with the use of the bicarbonate-centered approach. Stewart recognized that his analysis could not deal with the secondary responses to disruptions in acid–base homeostasis. Contrary to Seifter's assertion, all acid–base abnormalities can be diagnosed and interpreted with the bicarbonate-centered approach, and insights into their pathophysiology can be understood without adding the complexity of strong ion analysis.

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DOI: 10.1056/NEJMc1414731

TO THE EDITOR: As supporters of the Stewart approach,[1] we appreciate the fact that Seifter's clear explanation of these complex disorders does not take sides in the old quarrel between the traditional and physicochemical approaches.[2] However, we would like to point out a small error in the reasoning behind the effect of balanced solutions on acid–base equilibrium. It is not true that the use of Ringer's lactate with an in vivo strong ion difference of 29 mmol per liter could lead to metabolic acidosis in patients with normal acid–base status. On the contrary, it would lead to a slight metabolic alkalosis. An intuitive explanation is that the total concentration of weak acids such as albumin and phosphate — an acidifying entity that Stewart called A_{tot} — will also be diluted by the infusion. Morgan et al.[3] showed independently and Carlesso et al.[4] showed mathematically and experimentally that the strong ion difference of a crystalloid required to maintain unmodified baseline pH (in a patient with a normal level of bicarbonate) is 24 mmol per liter.

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1414731

TO THE EDITOR: Berend et al.[1] reviews the physiological approach and Seifter reviews the strong ion approach to assessment of acid–base disturbances. There is an interesting intersection between these models relating to the albumin-corrected anion gap. As both articles noted, in the physiological approach, the anion gap must be corrected for the concentration of albumin. The Figge–Jabor–Kazda–Fencl equation[2] for calculating the albumin-corrected anion gap is:

$$\text{Albumin-corrected anion gap} = \text{anion gap} + z \times ([\text{normal albumin}] - [\text{observed albumin}]);$$

where [normal albumin] and [observed albumin] are expressed in grams per deciliter, the albumin-corrected anion gap and the anion gap are expressed in millimoles per liter, and z is the net negative charge (expressed in millimoles per liter) contributed by each gram per deciliter of albumin concentration (including the charge contributed by bound calcium). The variable, z, can be derived with the use of an extension of the strong ion model in which albumin is treated as a polybasic macromolecule with many equilibrium dissociation constants corresponding to various classes of amino acid side chains.[3] By accounting for the charge on albumin,[3] including bound calcium,[4] the model yields a value of 2.3 to 2.5 for z as pH ranges from 7.2 to 7.5, and the level of ionized calcium ranges from 1.12 to 1.40 mmol per liter (Table 1).

Table 1. Calculated Values of z for Use in the Figge–Jabor–Kazda–Fencl Equation.*

Ionized Calcium (mmol/liter)	pH			
	7.2	7.3	7.4	7.5
1.12	2.3	2.4	2.5	2.5
1.26	2.3	2.3	2.4	2.5
1.40	2.3	2.3	2.4	2.5

* The variable z is the net negative charge (in millimoles per liter) contributed by each gram per deciliter of albumin concentration (including the charge contributed by bound calcium).

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DOI: 10.1056/NEJMc1414731

TO THE EDITOR: Seifter discusses some concepts introduced by Stewart's novel approach to acid–base analysis.[1,2] Figure 1 of the article shows sodium, chloride, potassium, bicarbonate, and hydrogen ions moving from blood into cells and from cells into the tubular lumen, with chloride being exchanged for bicarbonate or potassium exchanged for hydrogen ions. Unfortunately, this representation ignores simple stoichiometric issues. For example, the hydrogen ion concentration is expressed in nanomoles per liter, whereas chloride, sodium, and potassium concentrations are each expressed in millimoles per liter, a million times greater. Moreover and perhaps more importantly, the figure ignores the renal implications of Stewart's model — there is no such exchange. Changes in the measured urinary hydrogen ion and urinary bicarbonate concentrations simply reflect changes in the state of dissociation of carbon dioxide–containing urinary water, which follow alterations in the luminal strong ion difference induced by electrolyte movement. This is the key iconoclastic implication of Stewart's message: the porter–antiporter theory of tubular luminal hydrogen ion and bicarbonate concentrations is an illusion created by changes in the dissociation of water and carbon dioxide in water.

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DOI: 10.1056/NEJMc1414731

THE AUTHOR REPLIES: These letters illustrate the sharp dispute between two models for analyzing acid–base disorders. Boron and Vaughan-Jones's support of the bicarbonate-centered approach rests on experimental and theoretical considerations; Androgué and Gennari's approach rests on clinical interpretation. Boron and Vaughan-Jones propose that the strong ion difference does not alter pH; however, adding sodium bicarbonate at a constant level of carbon dioxide to a sodium chloride solution increases both the strong ion difference and the pH. They further claim that the strong ion difference, but not pH, changes with the addition of sodium lactate to sodium chloride solutions. However, lactate in the beaker, like chloride, acts as a strong ion, so that the mixture would not be expected to change the strong ion difference. It is the metabolism of lactate to bicarbonate in the body that increases the strong ion difference and has an alkalinizing effect. This point applies to the correct observation by Van Regenmortel et al. that acidosis associated with infused Ringer's lactate is unusual, but the alkalinizing effect of Ringer's lactate requires lactate metabolism.

Although I did not propose a mechanism for sensing the strong ion difference, as stated by Boron and Vaughan-Jones, I recognize a role for strong ions such as sodium, potassium, and calcium, as well as charge and hydrogen itself, in pH regulation.

In disputing the findings of studies by Figge, Fencl et al.,[1] and others, Androgué and Gennari exemplify the consequences of neglecting other charged species such as chloride and albumin, while they reference their own review[2] that mistakenly attributes normochloremic alkalosis with hypoalbuminemia to diuretic-induced alkalosis. The contribution of hypernatremia to acid–base disorders depends on the accompanying anion, with differences expected according to the administration of either hypertonic sodium chloride or sodium bicarbonate. Furthermore, since the sodium level but not the anion concentration is osmoregulatory, the relative concentration difference between the sodium level and the chloride level is important.

At the opposite end of the spectrum, Bellomo and Kellum deny the presence of antiporters, such as sodium–hydrogen and chloride–bicarbonate exchange, which are shown in Figure 1 of my article and supported by the substantial contributions of Boron[3] and others. I do not agree that these mechanisms are an illusion; rather, they demonstrate the interdependence of acid–base balance and electrolyte balance and constitute common ground for the two opposing camps.

It is interesting that the statement by Androgué and Gennari that "strong ions, weak acids, and carbon dioxide determine the bicarbonate concentration and pH" in a beaker contradicts the

interpretation by Boron and Vaughan-Jones that "changes in the strong ion difference are a consequence of adding acid and base as strong-ion salts; they do not cause pH to change." The debate about cause and effect and fact and opinion is really a debate about interpretation, given that causation is notoriously difficult to prove.[4]

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Since publication of his article, the author reports no further potential conflict of interest.

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DOI: 10.1056/NEJMc1414731

Hidden Formaldehyde in E-Cigarette Aerosols

TO THE EDITOR: E-cigarette liquids are typically solutions of propylene glycol, glycerol, or both, plus nicotine and flavorant chemicals. We have observed that formaldehyde-containing hemiacetals, shown by others to be entities that are detectable by means of nuclear magnetic resonance (NMR) spectroscopy,[1] can be formed during the e-cigarette "vaping" process. Formaldehyde is a known degradation product of propylene glycol that reacts with propylene glycol and glycerol during vaporization to produce hemiacetals (Fig. 1). These molecules are known formaldehyde-releasing agents that are used as industrial biocides.[5] In many samples of the particulate matter (i.e., the aerosol) in "vaped" e-cigarettes, more than 2% of the total solvent molecules have converted to formaldehyde-releasing agents, reaching concentrations higher than concentrations of nicotine. This happens when propylene glycol and glycerol are heated in the presence of oxygen to temperatures reached by commercially available e-cigarettes operating at high voltage. How formaldehyde-releasing agents behave in the respiratory tract is unknown, but formaldehyde is an International Agency for Research on Cancer group 1 carcinogen.[4]

Here we present results of an analysis of commercial e-liquid vaporized with the use of a "tank system" e-cigarette featuring a variable-voltage battery. The aerosolized liquid was collected in an NMR spectroscopy tube (10 50-ml puffs over 5 minutes; 3 to 4 seconds per puff). With each puff, 5 to 11 mg of e-liquid was consumed, and 2 to 6 mg of liquid was collected. At low voltage (3.3 V), we did not detect the formation of any formaldehyde-releasing agents (estimated limit of detection, approximately 0.1 μg per 10 puffs). At high voltage (5.0 V), a mean (±SE) of 380±90 μg per sample (10 puffs) of formaldehyde was detected as formaldehyde-releasing agents. Extrapolating from the results at high voltage, an e-cigarette user vaping at a rate of 3 ml per day would inhale 14.4±3.3 mg of formaldehyde per day in formaldehyde-releasing agents. This estimate is conservative because we did not collect all of the aerosolized liquid, nor did we collect any gas-phase formaldehyde. One estimate of the average delivery of formaldehyde from conventional cigarettes is approximately 150 μg per cigarette,[3] or 3 mg per pack of 20 cigarettes. Daily exposures of formaldehyde associated with cigarettes, e-cigarettes from the formaldehyde gas phase, and e-cigarettes from aerosol particles containing formaldehyde-releasing agents are shown in Figure 1.

Inhaled formaldehyde has a reported slope factor of 0.021 mg per kilogram of body weight per day for cancer (http://oehha.ca.gov/risk/pdf/TCDBcas061809.pdf). This slope factor was calculated as follows: [the kilograms of body weight × the number of days of formaldehyde exposure] ÷ the milligrams of formaldehyde. Among persons with a body weight of 70 kg, the incremental lifetime cancer risk associated with long-term cigarette smoking at 1 pack per day may then be estimated at 9×10^{-4}. If we assume that inhaling formaldehyde-releasing agents carries the same risk per unit of formaldehyde as the risk associated with inhaling gaseous formaldehyde, then long-term vaping is associated with an incremental lifetime cancer risk of 4.2×10^{-3}. This risk is 5 times as high (as compared with the risk based on the calculation of Miyake and Shibamoto shown in Fig. 1), or even 15 times as high (as compared with the risk based on the calculation of Counts et al. shown