To be or Not to be a Pharmaceutical Hazardous Waste

That is the Question

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AGENDA

Statement of problem

Definition of hazardous waste

Evaluation method – Chemistry review

- Hemoglobin microcuvette
- Glucose microcuvette

Conclusions

References

Problem: HemoCue™ Hb 201 DM Microcuvette Hazardous Waste – how to evaluate?

- The HemoCue™ Hb 201DM is used for the determination of the total amount of hemoglobin in whole blood.
- The specially designed microcuvette contains dried reagents.
- ***Is this a Hazardous Waste?***

Definition of a Hazardous Waste

Characteristic

1. **Ignitable** – a liquid with a flash point below 140 degree Fahrenheit
2. **Oxidizer** – a substance that supplies oxygen to a reaction in the absence of air
3. **Corrosive** – a liquid with a pH of 2 or less or 12.5 or more
4. **Reactive** – a substance that is unstable, or can react violently, produce toxic gases, or form potentially explosive mixtures when mixed with water
5. **Toxic** – a waste that will leach hazardous contaminants above the maximum allowable concentrations as specified in the TCLP contaminants table

Listed

Ingredients as listed on one of the four hazardous waste lists: F, P, K and U

MN Lethal

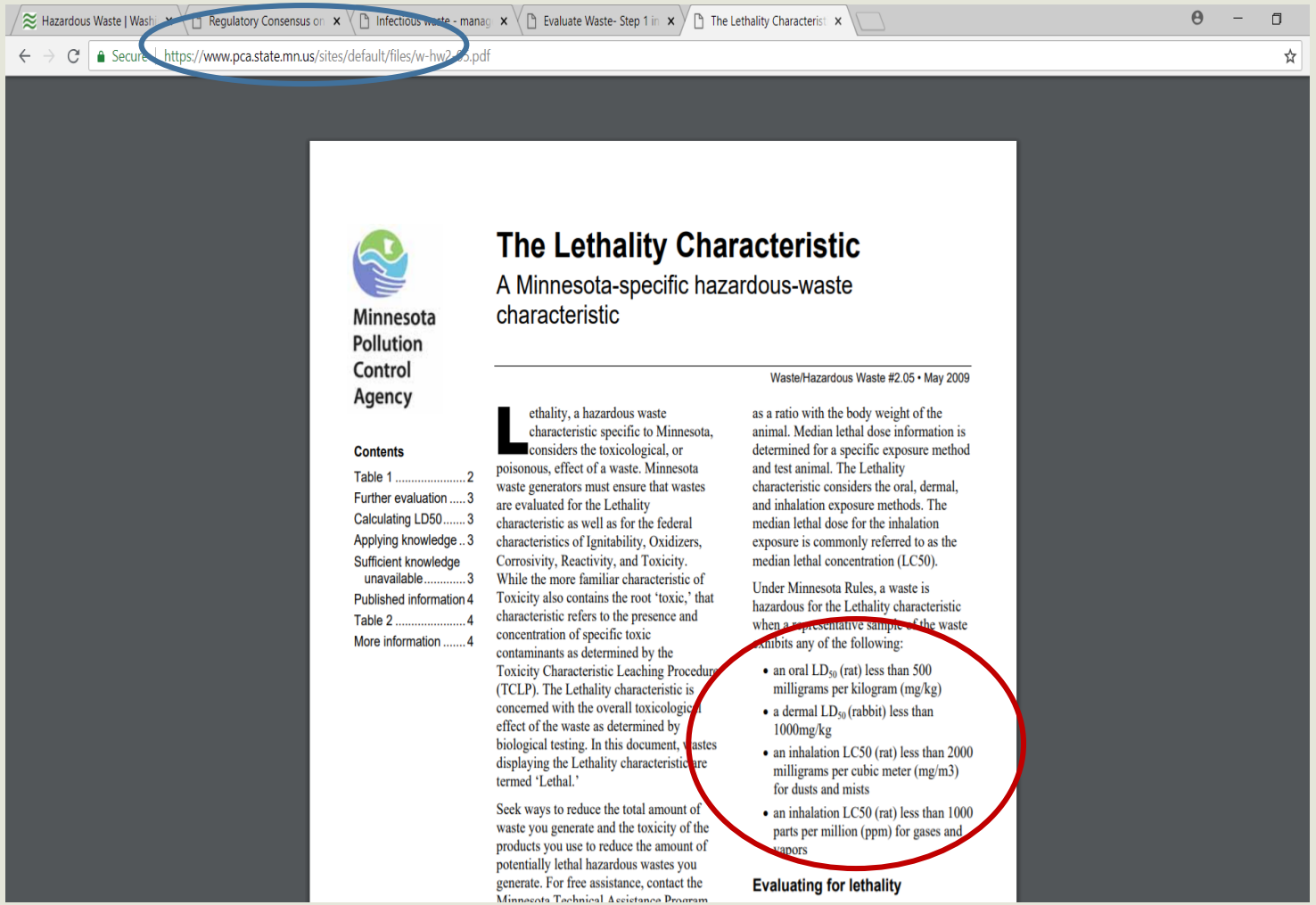
A characteristic category specific to MN, a waste if its oral or dermal LD50 or inhalation concentration LC50 is less than the hazardous waste threshold specific to MN

See The Lethality Characteristic factsheet for more detail.

All waste in MN is considered HAZARDOUS until evaluated and determined otherwise.

MN Lethal if:

- LD50 oral rat < 500 mg/kg
- LD50 dermal rabbit < 1,000 mg/kg
- LC50 inhalation rat < 1,000 ppm for gases and vapors



Hazardous Waste | Washi… | Regulatory Consensus on… | Infectious waste - manag… | Evaluate Waste- Step 1 in… | The Lethality Characterist…

https://www.pca.state.mn.us/sites/default/files/w-hw2-05.pdf

Minnesota Pollution Control Agency

The Lethality Characteristic

A Minnesota-specific hazardous-waste characteristic

Waste/Hazardous Waste #2.05 • May 2009

Contents

Lethality, a hazardous waste characteristic specific to Minnesota, considers the toxicological, or poisonous, effect of a waste. Minnesota waste generators must ensure that wastes are evaluated for the Lethality characteristic as well as for the federal characteristics of Ignitability, Oxidizers, Corrosivity, Reactivity, and Toxicity. While the more familiar characteristic of Toxicity also contains the root 'toxic,' that characteristic refers to the presence and concentration of specific toxic contaminants as determined by the Toxicity Characteristic Leaching Procedure (TCLP). The Lethality characteristic is concerned with the overall toxicological effect of the waste as determined by biological testing. In this document, wastes displaying the Lethality characteristic are termed 'Lethal.'

Seek ways to reduce the total amount of waste you generate and the toxicity of the products you use to reduce the amount of potentially lethal hazardous wastes you generate. For free assistance, contact the Minnesota Technical Assistance Program

as a ratio with the body weight of the animal. Median lethal dose information is determined for a specific exposure method and test animal. The Lethality characteristic considers the oral, dermal, and inhalation exposure methods. The median lethal dose for the inhalation exposure is commonly referred to as the median lethal concentration (LC50).

Under Minnesota Rules, a waste is hazardous for the Lethality characteristic when a representative sample of the waste exhibits any of the following:

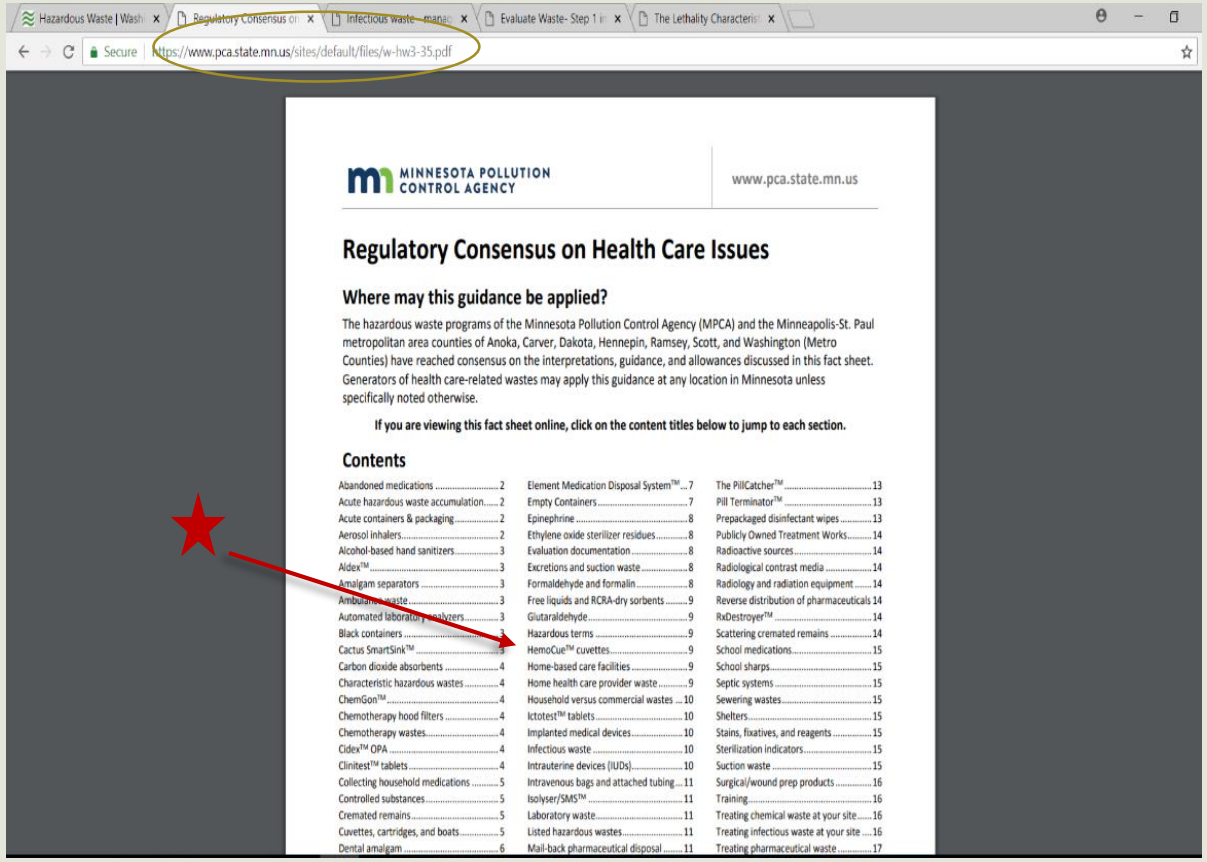
- an oral LD_{50} (rat) less than 500 milligrams per kilogram (mg/kg)
- a dermal LD_{50} (rabbit) less than 1000mg/kg
- an inhalation LC50 (rat) less than 2000 milligrams per cubic meter (mg/m3) for dusts and mists
- an inhalation LC50 (rat) less than 1000 parts per million (ppm) for gases and vapors

Evaluating for lethality

MPCA Factsheet – Guidance Document

★ HemoCue cuvettes

★ "assume to be MN Lethal HW unless evaluated as non-hazardous"



MINNESOTA POLLUTION CONTROL AGENCY

www.pca.state.mn.us

Regulatory Consensus on Health Care Issues

Where may this guidance be applied?

The hazardous waste programs of the Minnesota Pollution Control Agency (MPCA) and the Minneapolis-St. Paul metropolitan area counties of Anoka, Carver, Dakota, Hennepin, Ramsey, Scott, and Washington (Metro Counties) have reached consensus on the interpretations, guidance, and allowances discussed in this fact sheet. Generators of health care-related wastes may apply this guidance at any location in Minnesota unless specifically noted otherwise.

If you are viewing this fact sheet online, click on the content titles below to jump to each section.

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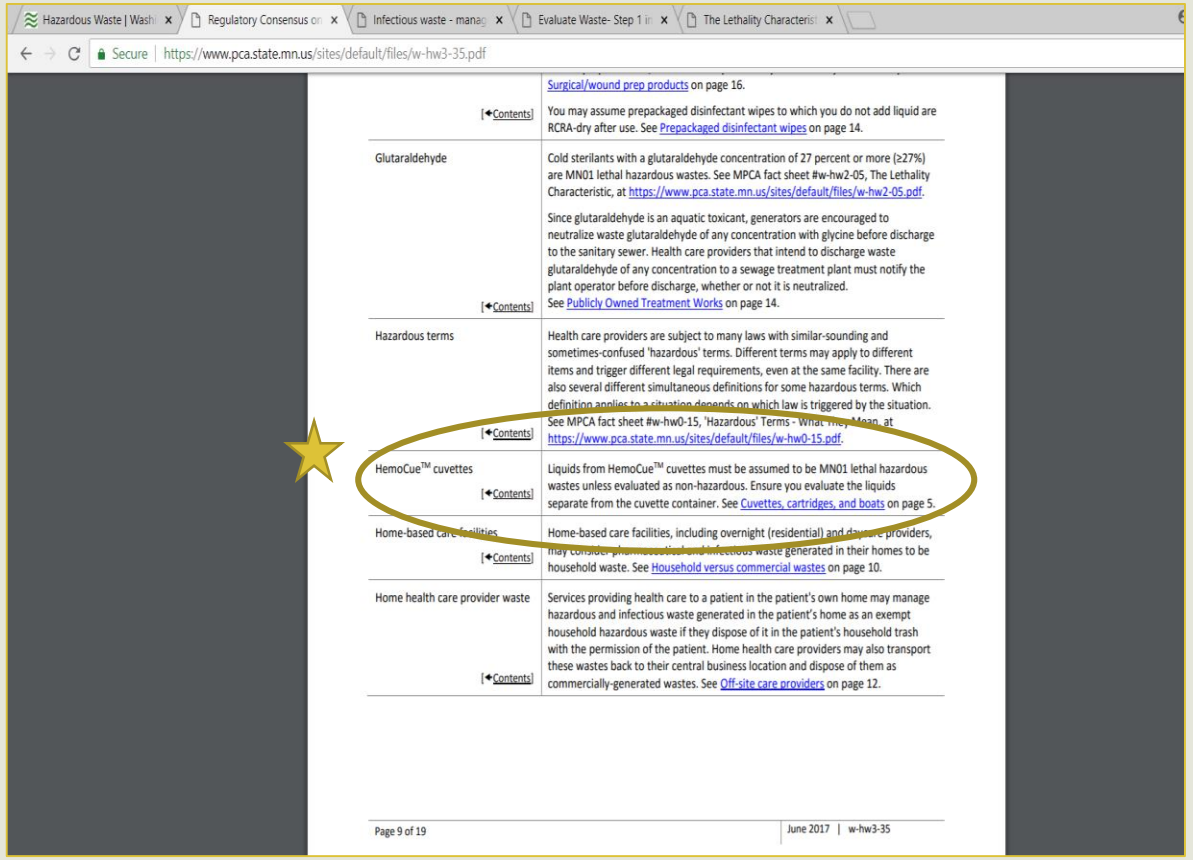

Surgical/wound prep products on page 16.

[Contents]

You may assume prepackaged disinfectant wipes to which you do not add liquid are RCRA-dry after use. See Prepackaged disinfectant wipes on page 14.

Glutaraldehyde

Cold sterilants with a glutaraldehyde concentration of 27 percent or more (≥27%) are MN01 lethal hazardous wastes. See MPCA fact sheet #w-hw2-05, The Lethality Characteristic, at https://www.pca.state.mn.us/sites/default/files/w-hw2-05.pdf.

Since glutaraldehyde is an aquatic toxicant, generators are encouraged to neutralize waste glutaraldehyde of any concentration with glycine before discharge to the sanitary sewer. Health care providers that intend to discharge waste glutaraldehyde of any concentration to a sewage treatment plant must notify the plant operator before discharge, whether or not it is neutralized. See Publicly Owned Treatment Works on page 14.

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Hazardous terms

Health care providers are subject to many laws with similar-sounding and sometimes-confused 'hazardous' terms. Different terms may apply to different items and trigger different legal requirements, even at the same facility. There are also several different simultaneous definitions for some hazardous terms. Which definition applies to a situation depends on which law is triggered by the situation. See MPCA fact sheet #w-hw0-15, 'Hazardous' Terms - What They Mean, at https://www.pca.state.mn.us/sites/default/files/w-hw0-15.pdf.

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HemoCue™ cuvettes

Liquids from HemoCue™ cuvettes must be assumed to be MN01 lethal hazardous wastes unless evaluated as non-hazardous. Ensure you evaluate the liquids separate from the cuvette container. See Cuvettes, cartridges, and boats on page 5.

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Home-based care facilities

Home-based care facilities, including overnight (residential) and daytime providers, may consider pharmaceutical and infectious waste generated in their homes to be household waste. See Household versus commercial wastes on page 10.

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Home health care provider waste

Services providing health care to a patient in the patient's own home may manage hazardous and infectious waste generated in the patient's home as an exempt household hazardous waste if they dispose of it in the patient's household trash with the permission of the patient. Home health care providers may also transport these wastes back to their central business location and dispose of them as commercially-generated wastes. See Off-site care providers on page 12.

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Steps to waste evaluation

Step 1

Ingredients

- SDS
- Chemical composition from manufacturer

Step 2

Ingredient meet HW definition?

- Characteristic?
- Lethal?
- Listed?

Step 3

Apply Chemistry

- Literature search
- Reactions?
- Residuals?

Step 4

Evaluate Residual

- Does the end result in a characteristic or lethal hazardous waste?
- Document findings

Ingredients of the HemoCue Hb cuvette*

STEP 1: List the ingredients:

STEP 2: Meet the definition:

Ingredient	LD_{50} oral rat	Wt %	Hazardous?
Sodium deoxycholate	1370	<0.3%	NO
Sodium azide	27	<0.14%	**YES**
Sodium nitrite	180	<0.06%	**YES**
Polystyrene microcuvette body	NA	>99.6	NA

* HemoCue® Safety Data Sheet (Revision date: 12Aug2015)

Apply the Chemistry

Step 3

Problem: HemoCue™ Hb 201 DM Microcuvette How to evaluate?

- The HemoCue™ Hb 201DM is used for the determination of the total amount of hemoglobin in whole blood.

- Blood (5 µL) is drawn into the cavity by capillary action and is spontaneously mixed with the reagents for the test.

Step 3: Apply the Chemistry

Mechanism of action for hemoglobin determination

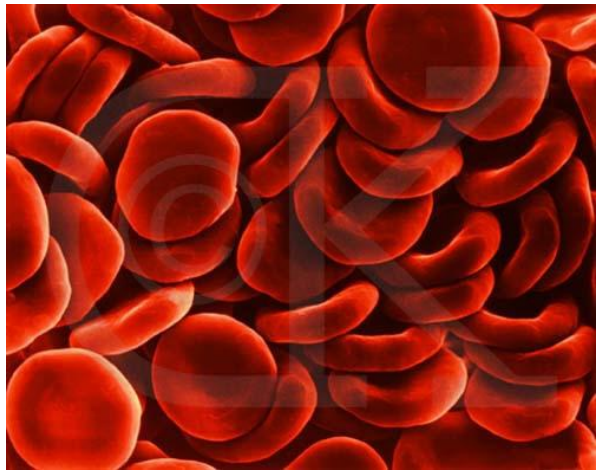
- Hemoglobin is released from the erythrocytes by sodium deoxychloate
- Sodium nitrite oxidizes hemoglobin iron from the ferrous (Fe^{II}) ion to ferric (Fe^{III}) ion to form methemoglobin and nitric oxide (NO)
- The ferric methemoglobin reacts with sodium azide to form azidomethemoglobin

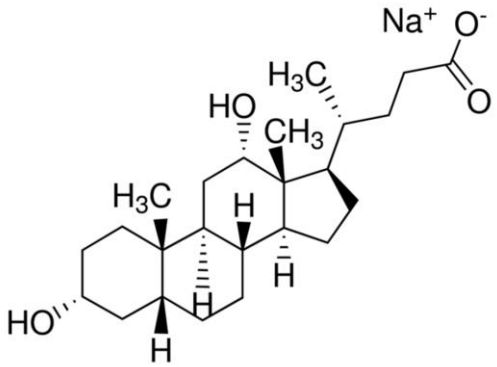
QUESTION: How do the MN lethal ingredients
- sodium nitrite and sodium azide -
react in the HemoCue Hb microcuvette with the blood?

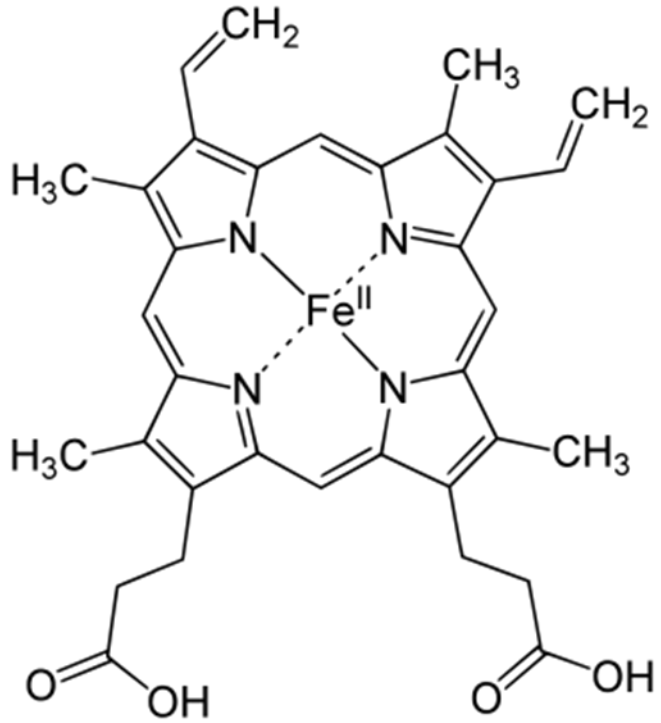
Both the sodium nitrite and the sodium azide react with the iron in the hemoglobin and are consumed during the Hb test

- The test strip uses 5 µL of blood
- Calculate how many moles of Fe(II) are in 5 µL of blood
- Calculate residual sodium azide and sodium nitrite after reaction with Fe(II)

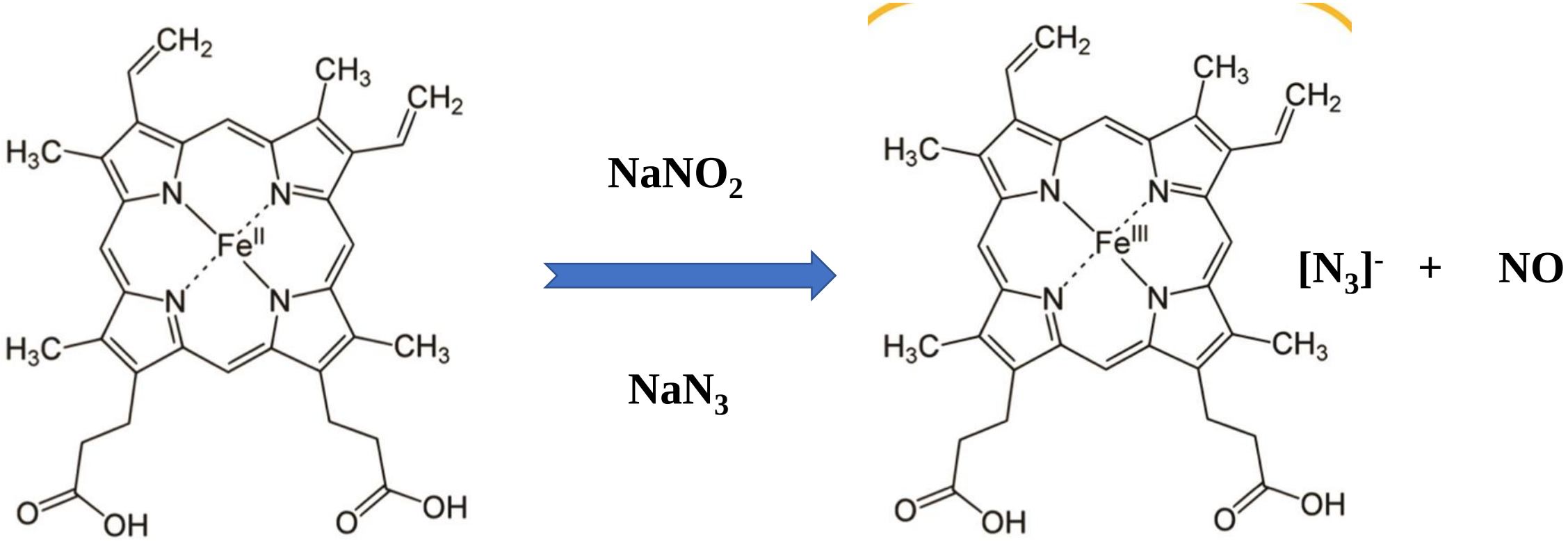
1. Hemolysis of erythrocytes







2. Oxidation of hemoglobin to methemoglobin



The HemoCue microcuvette uses $5\,\mu L$ ($0.005\,mL$) blood

Blood contains approximately $13\,g\ Fe$ / $100\,mL$ blood

Determine the number of moles of Fe in $5\,\mu L$ of blood

$$\#\ mol\ Fe = 5\,\mu L\ blood * \frac{13\,g\ Fe}{100\,mL\ blood} * \frac{1\,mL\ blood}{1000\,\mu L\ blood} * \frac{1\ mol\ Fe}{55.845\,g\ Fe}$$

$$= 1.16 \times 10^{-5}\ mol\ Fe$$

One microcuvette weighs ~ 0.66 g

Sodium nitrite is 0.16 wt % of the microcuvette

Calculate # of moles $NaNO_2$ / microcuvette

$$\#\,mol\ NaNO_2 = 0.66\,g\ cuvette \times \frac{0.0016\,g\ NaNO_2}{1.0\,g\ cuvette} \times \frac{1\ mol\ NaNO_2}{69\,g\ NaNO_2}$$

$$= 1.53 \times 10^{-5}\ mol\ NaNO_2 / cuvette$$

One microcuvette weighs ~ 0.66 g

Sodium azide is 0.14 wt% of the microcuvette

Calculate # of mole of NaN_3/microcuvette

$$\#\,mol\ NaN_3 = 0.66\,g\ cuvette * \frac{0.0014\,g\ NaN_3}{1.0\,g\ cuvette} * \frac{1\,mol\ NaN_3}{65\,g\ NaN_3}$$

$$= 1.42 \times 10^{-5}\ mol\ NaN_3/cuvette$$

Steps to waste evaluation

Step 1

Ingredients

- SDS
- Chemical composition from manufacturer

Step 2

Ingredient meet HW definition?

- Characteristic?
- Lethal?
- Listed?

Step 3

Apply Chemistry

- Literature search
- Reactions?
- Residuals?

Step 4: Evaluate Residual

- **Result a characteristic or lethal hazardous waste?**
- **Document findings**

Step 4: Evaluate the Residuals

Component	Wt (g) (initial)	Wt (g) (final)	Wt % (final)*
Polystyrene microcuvette body	0.66	0.66	
Sodium deoxycholate			
Sodium azide	0.000923	0.000169	0.026
Sodium nitrite	0.00106	0.000255	0.015
Non-reactive ingredients	NA	NA	

Wt % (final) = wt (g) (final) / 0.66 g

Minnesota Pollution Control Agency

The Lethality Characteristic

A Minnesota-specific hazardous-waste characteristic

Waste/Hazardous Waste #2.05 • May 2009

Contents

Lethality, a hazardous waste characteristic specific to Minnesota, considers the toxicological, or poisonous, effect of a waste. Minnesota waste generators must ensure that wastes are evaluated for the Lethality characteristic as well as for the federal characteristics of Ignitability, Oxidizers, Corrosivity, Reactivity, and Toxicity. While the more familiar characteristic of Toxicity also contains the root 'toxic,' that characteristic refers to the presence and

as a ratio with the body weight of the animal. Median lethal dose information is determined for a specific exposure method and test animal. The Lethality characteristic considers the oral, dermal, and inhalation exposure methods. The median lethal dose for the inhalation exposure is commonly referred to as the median lethal concentration (LC50).

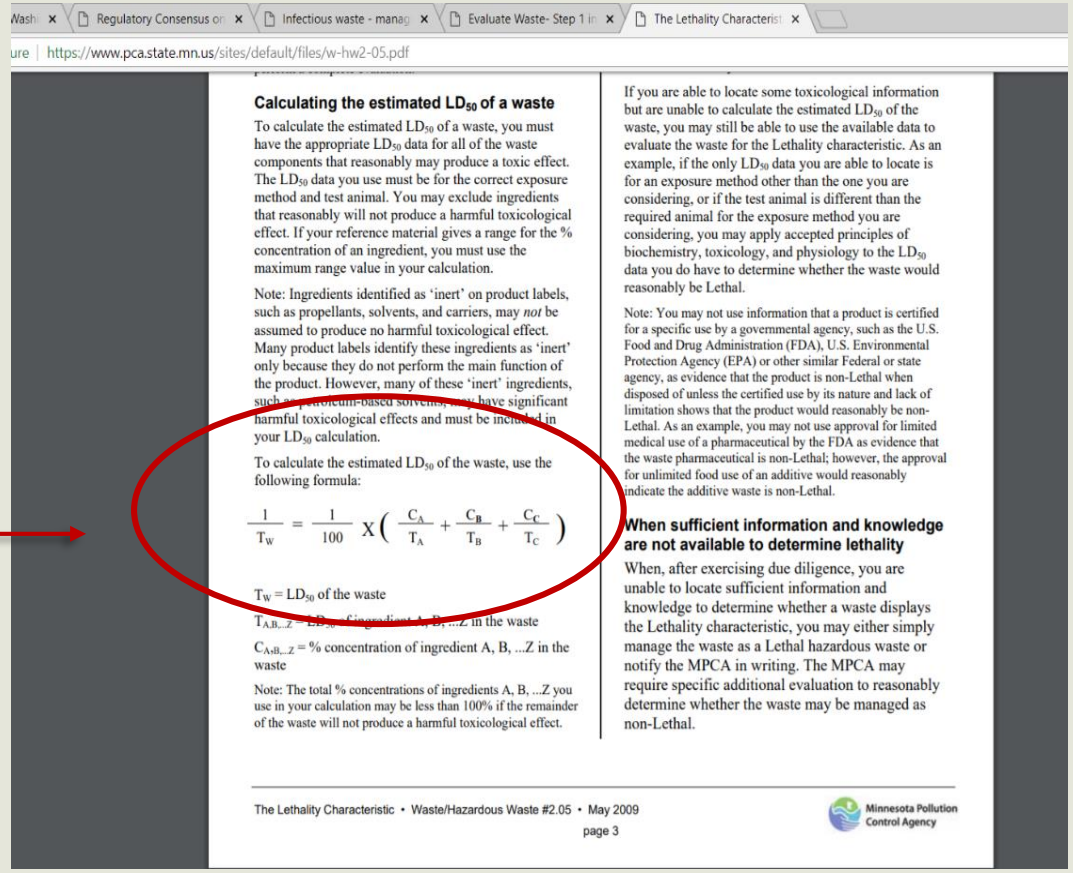
Under Minnesota Rules, a waste is hazardous for the Lethality characteristic when a representative sample of the waste

Calculate the estimated LD50 of a waste

From the MPCA factsheet:

The Lethality Characteristic

Calculate the estimated LD50 of the waste, use the formula



Regulatory Consensus on | Infectious waste - manag | Evaluate Waste- Step 1 in | The Lethality Characterist

https://www.pca.state.mn.us/sites/default/files/w-hw2-05.pdf

Calculating the estimated LD_{50} of a waste

To calculate the estimated LD_{50} of a waste, you must have the appropriate LD_{50} data for all of the waste components that reasonably may produce a toxic effect. The LD_{50} data you use must be for the correct exposure method and test animal. You may exclude ingredients that reasonably will not produce a harmful toxicological effect. If your reference material gives a range for the % concentration of an ingredient, you must use the maximum range value in your calculation.

Note: Ingredients identified as 'inert' on product labels, such as propellants, solvents, and carriers, may *not* be assumed to produce no harmful toxicological effect. Many product labels identify these ingredients as 'inert' only because they do not perform the main function of the product. However, many of these 'inert' ingredients, such as petroleum-based solvents, may have significant harmful toxicological effects and must be included in your LD_{50} calculation.

To calculate the estimated LD_{50} of the waste, use the following formula:

$$\frac{1}{T_W} = \frac{1}{100} X \left(\frac{C_A}{T_A} + \frac{C_B}{T_B} + \frac{C_C}{T_C} \right)$$

T_W = LD_{50} of the waste

$T_{A,B,...Z}$ = LD_{50} of ingredient A, B, ...Z in the waste

$C_{A,B,...Z}$ = % concentration of ingredient A, B, ...Z in the waste

Note: The total % concentrations of ingredients A, B, ...Z you use in your calculation may be less than 100% if the remainder of the waste will not produce a harmful toxicological effect.

If you are able to locate some toxicological information but are unable to calculate the estimated LD_{50} of the waste, you may still be able to use the available data to evaluate the waste for the Lethality characteristic. As an example, if the only LD_{50} data you are able to locate is for an exposure method other than the one you are considering, or if the test animal is different than the required animal for the exposure method you are considering, you may apply accepted principles of biochemistry, toxicology, and physiology to the LD_{50} data you do have to determine whether the waste would reasonably be Lethal.

Note: You may not use information that a product is certified for a specific use by a governmental agency, such as the U.S. Food and Drug Administration (FDA), U.S. Environmental Protection Agency (EPA) or other similar Federal or state agency, as evidence that the product is non-Lethal when disposed of unless the certified use by its nature and lack of limitation shows that the product would reasonably be non-Lethal. As an example, you may not use approval for limited medical use of a pharmaceutical by the FDA as evidence that the waste pharmaceutical is non-Lethal; however, the approval for unlimited food use of an additive would reasonably indicate the additive waste is non-Lethal.

When sufficient information and knowledge are not available to determine lethality

When, after exercising due diligence, you are unable to locate sufficient information and knowledge to determine whether a waste displays the Lethality characteristic, you may either simply manage the waste as a Lethal hazardous waste or notify the MPCA in writing. The MPCA may require specific additional evaluation to reasonably determine whether the waste may be managed as non-Lethal.

To calculate the estimated LD_{50} of the waste, use the following formula:

$$\frac{1}{T_W} = \frac{1}{100} X \left(\frac{C_A}{T_A} + \frac{C_B}{T_B} + \frac{C_C}{T_C} \right)$$

$T_W = LD_{50}$ of the waste

$T_{A,B,...Z} = LD_{50}$ of ingredient A, B, ...Z in the waste

$C_{A,B,...Z}$ = % concentration of ingredient A, B, ...Z in the waste

Note: The total % concentrations of ingredients A, B, ...Z you use in your calculation may be less than 100% if the remainder of the waste will not produce a harmful toxicological effect.

Residue of the HemoCue Hb cuvette meet the MN Lethal definition?

NO - nonhazardous

$$\frac{1}{T_W} = \frac{1}{100}\left(\frac{C_{NaN_3}}{T_{NaN_3}} + \frac{C_{NaNO_3}}{T_{NaNO_3}}\right)$$

$$\frac{1}{T_W} = \frac{1}{100}\left(\frac{0.026}{27} + \frac{0.015}{180}\right)$$

$$\frac{1}{T_W} = \frac{1}{100}\left(0.00096 + 0.000083\right)$$

$$\frac{1}{T_W} = \frac{0.00104}{100}$$

$$T_W = 96,153 \text{ mg/kg}$$

Reminder ~ MN Lethal if:

- LD_{50} oral rat < 500 mg/kg

SUMMARY

Determine if ingredients are hazardous or MN lethal

- Is the LD50 (oral rat) < 500 mg/kg?

Are hazardous materials consumed during the test protocol?

- Evaluate chemical reactions in test procedure

Do the residual components meet the definition of hazardous waste?

- Hazardous or Not?

HemoCue® Glucose 201 Microcuvette

Quick Review

HemoCue® Glucose 201 Microcuvette

- The HemoCue® Glucose 201 system is intended for quantitative determination of glucose in whole blood.
- The microcuvette uses 5 µL sample of whole blood that is drawn into a cavity that contains dry reagents uniformly deposited on the surface of the cavity.
- Blood is drawn into the cavity by capillary action and is spontaneously mixed with the reagents for the test.

HemoCue® Glucose 201 Microcuvette *

* HemoCue® Safety Data Sheet (Revision date: 12Aug2015)

STEP 1: List the ingredients:

Ingredient	LD_{50} oral rat	Wt %
Polystyrene microcuvette body	NA	99.9
Saponin (EPA PC Code 097095*)	> 3000*	<0.02
Polypropylene glycol	20,000	<0.01
Enzyme mix (diaphorase, GHD, mutarotase, NAD)	20,000	<0.02
MTT, ammonium chloride, sodium fluoride	52??	<0.02

STEP 2: Meet the definition:

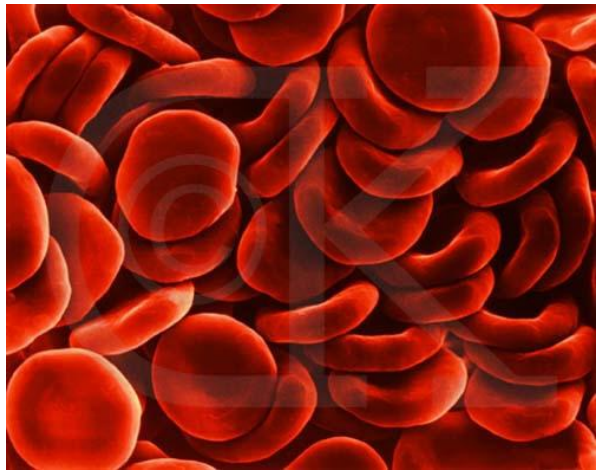
Hazardous?
NO
NO
NO
NO
??

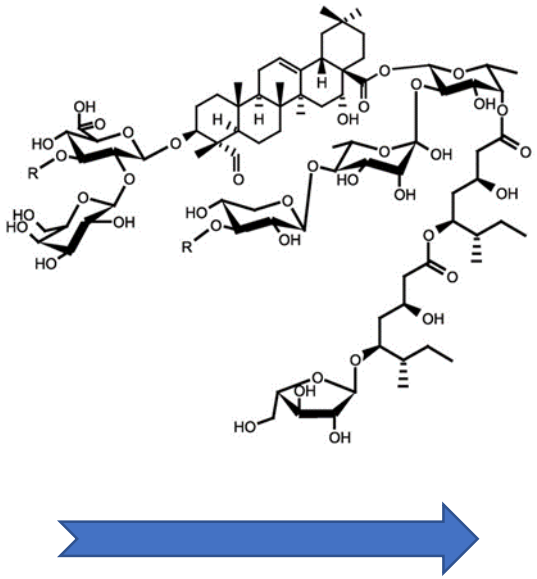
Step 3: Apply the Chemistry

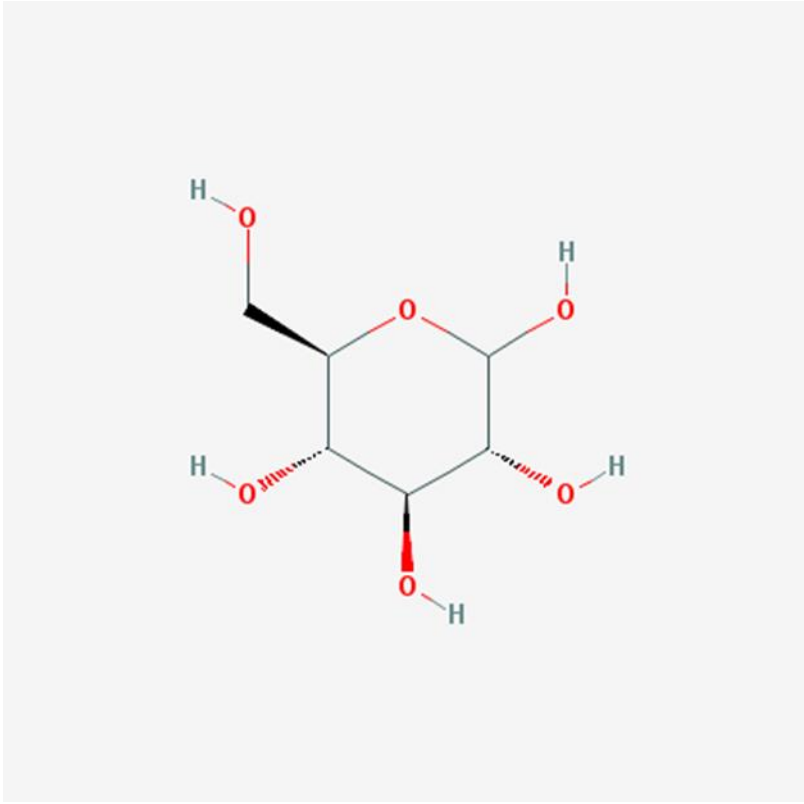
Mechanism of action for hemoglobin determination

- Glucose is released from the erythrocytes by saponin
  - Complexes with cholesterol to form pores to release glucose
- α-D-glucose converted to β-D-glucose
- β-D-glucose is oxidized to form NADH
- NADH reacts with diaphorase in the presence of MTT to afford a highly colored formazan salt

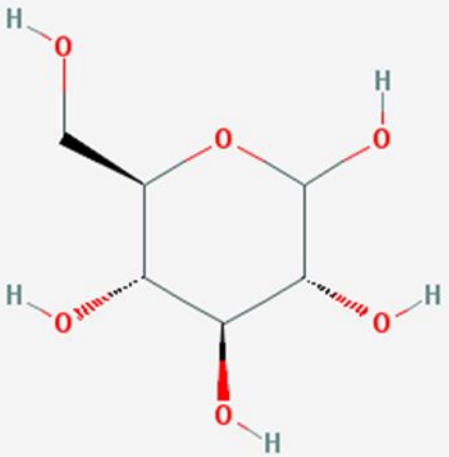
1. Hemolysis of erythrocytes to release glucose



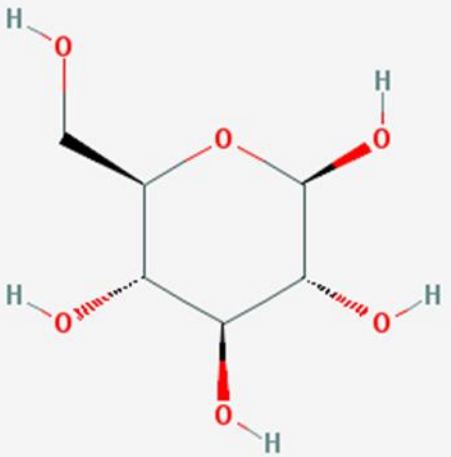




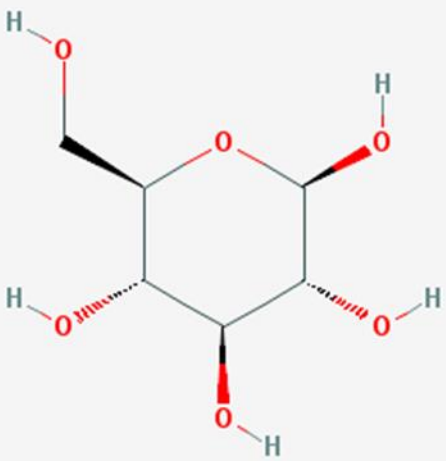
2. Rearrangement of α-D-glucose to β-D-glucose



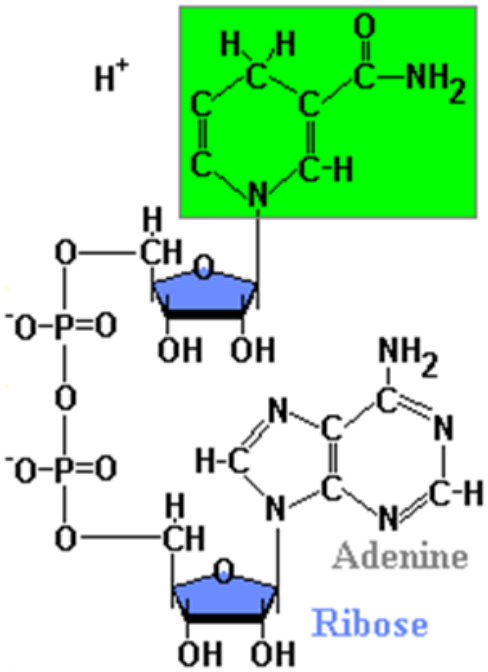
mutarotase



3. Dehydration of β-D-glucose to NADH

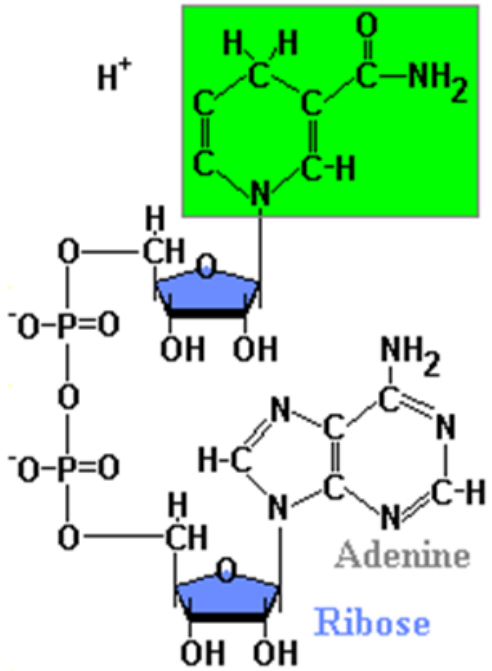


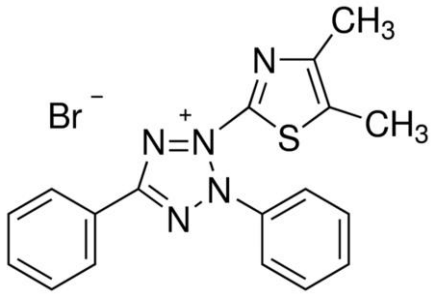
glucose dehydrogenase



NADH + H^+

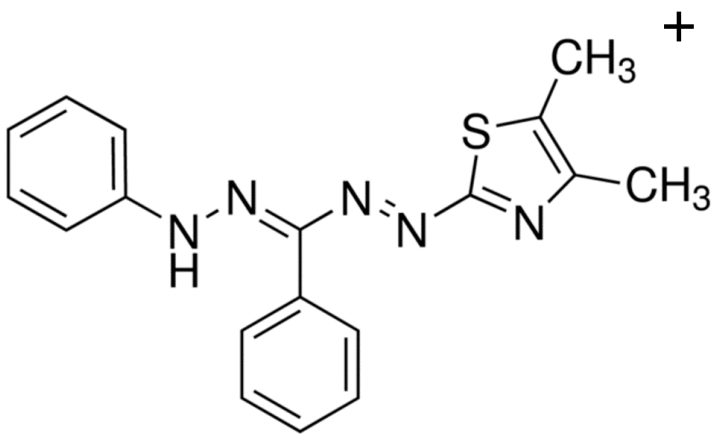
3. Formation of [formazan]$^{+}$ [NADH]$^{-}$





diaphorase

NADH^{-}



+ Br^{-}

Saponin toxicity documentation

- Merck Index 11th Edition, page 1328, 1989.
  - **8328. Saponins.** Sapogenin glycosides: "Although practically non-toxic to man upon oral ingestion, they act as powerful hemolytics when injected into the blood stream, dissolving the red corpuscles even at extreme dilution."
- http://www.pesticideinfo.org/Detail_Chemical.jsp?Rec_Id=PC35915 (accessed 10Oct2018)
  - Saponin: CAS # 8047-15-2
- Biopesticide Registration Action Document (EPA PC Code 097095, 14Jul2007)
  - Mode of action: inhibits growth pathogenic fungi and nematodes

TABLE 3. Mammalian toxicity requirements for saponins of *Quillaja saponaria*[1]

Study/OPPTS Guideline No.	Results	Toxicity category	MRID No.
Acute oral toxicity (870.1100)	LD_{50} >3000 mg product/kg **Acceptable**	III	46608101
Acute dermal toxicity (870.1200)	LD_{50} >4000 mg product/kg **Acceptable**	III	46608102
Acute inhalation toxicity (870.1300)	LC_{50} >2 mg product/L **Acceptable**	IV	46774901
Primary eye irritation (870.2400)	Corneal opacity was noted on 3/3 rabbits at 24 hrs post-instillation with symptoms clearing on one rabbit by 48 hrs, on another rabbit by 72 hrs, and persistence on the third rabbit through 72 hrs. **Acceptable**	I[2]	46608103
Primary dermal irritation(870.2500)	Very slight erythema was noted on 3/3 rabbits one hour after patch removal, with clearance on one rabbit by 24 hrs and on two rabbits by 48 hrs; not an irritant. **Acceptable**	IV	46608104

U.S. Environmental Protection Agency
Office of Pesticide Programs
Biopesticides and Pollution Prevention Division
Biochemical Pesticides Branch

SAPONINS OF *QUILLAJA SAPONARIA*

(PC Code **097095**)

http://www.pesticideinfo.org/Detail_Chemical.jsp?Rec_Id=PC35915

saponin toxicity - Yahoo Search ... | Saponin - toxicity, ecological ...

YourCause | YouTube | https--mail.google

Detailed Toxicity Information

Acute Toxicity [2]	Saponin
WHO Acute Hazard	Not Listed
TRI Acute Hazard	Not Listed
Material Safety Data Sheets	Not Available
Acute rating from U.S. EPA product label	No Consensus Value
U.S. NTP Acute Toxicity Studies	No NTP Studies
View Studies	
Cholinesterase Inhibitor	No

2. The acute toxicity reported on this page is of the pure chemical ingredient only and may not reflect the acute toxicity of in section above.

Cancer Information	Saponin
IARC Carcinogens	Not Listed
U.S. NTP Carcinogens	Not Listed
California Prop 65 Known Carcinogens	Not Listed
U.S. EPA Carcinogens	Not Listed
TRI Carcinogen	Not Listed

Endocrine Disruption	Saponin
Illinois EPA list	Not Listed
Keith list	Not Listed
Colborn list	Not Listed
Benbrook list	Not Listed
Danish Inert list	Not Listed
EU list	Not Listed

CONCLUSIONS

- Components of the **hemoglobin microcuvette** are involved in chemical reactions:
  - Sodium deoxycholate interacts with the erythrocyte cell wall to release hemoglobin
  - Sodium nitrite oxidizes Fe^{II} in hemoglobin to Fe^{III} in methemoglobin and forms a highly colored azide salt
- Components of the **glucose microcuvette** are involved in chemical reactions:
  - Saponin interacts with the erythrocyte cell wall to release glucose
  - MTT bromide ring opens and forms a highly colored formazan salt with NADH

Basically the initial components are non-hazardous, therefore, the used and unused microcuvette are not hazardous waste

REFERENCES

- Banauch, et al., Z. Klin. Chem. U. Klin. Biochem., 1975; 7:101-107.
- Bergmeyer, Methods of Enzymatic Analysis, Vol 1, 136-144, Chemie Publishers, Weinheim.
- HemoCue® Glucose 201 Microcuvette, Safety Data Sheet, Revision date: 21Aug2015.
- HemoCue® Plasma/Low Hb Microcuvette, Safety Data Sheet, Revision date: 12Aug2015.
- Chingkuang, Tu, et al., Free Radic. Biol. Med., 2009, January 1; 46(1): 14-19
- Greenberg et al., J. Biol. Chem., 1943 151; 665-673.

Questions?

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Thank you!

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