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# Dichlorophenol Exposure and Chronic Kidney Disease

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Dichlorophenol Exposure and Chronic Kidney Disease

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### Abstract

**Purpose:** To explore the relationship between the common pesticides, 2,4-dichlorophenol (2,4-DCP) and 2,5-dichlorophenol (2,5-DCP) with serum creatinine as a biomarker of kidney function.

**Methods:** National Health and Nutrition Examination Survey (NHANES) 2013 to 2014 data ( $N = 2,063$ , 47% male and 53% female) was used to statistically analyze the relationship between either of two common pesticides 2,4-DCP or 2,5-DCP and serum creatinine levels. Gender stratified analysis was completed using multivariate adjusted linear regression. Variables adjusted were age, ethnicity and annual household income.

**Results:** In both males and females exposure to 2,4-DCP did not elevate serum creatinine and regression results were not significant. For 2,5-DCP exposure, serum creatinine was not significantly elevated in males. However, in females, 2,5-DCP exposure was associated with significant decrease in serum creatinine at  $p = .017$ .

**Conclusion:** These pesticides continue to be of human health concerns, and with varied results in both genders. Further testing is warranted.

*Keywords:* Pesticide, serum creatinine, gender stratification, statistical analysis, health concerns

### Dichlorophenol Exposure and Chronic Kidney Disease

Chronic Kidney Disease (CKD) is prevalent in agricultural (sugarcane) workers of Central America. These workers are not only developing CKD at much higher rates, causing mortality, but they are developing the disease at very early ages (Orantes-Navarro et al., 2017; Valcke, Levasseur, Soares da Silva, & Wesseling, 2017). The disease is not associated with hypertension or diabetes, but contributing factors are thought to be exposure to pesticides and or chronic heat exposure combined with heavy work load, consumption of non-steroidal anti-inflammatory (NSAIDs) and poor hydration coupled with excess consumption of high sugar beverages (Valcke et al., 2017). Since these countries are not as developed as the United States (U.S.), there is not the quick access to medical care and diagnosis, nor the ability to care for the large volume of patients that require medical treatment (Orantes-Navarro et al., 2017).

This project will evaluate CKD in sugarcane worker by conducting an extensive literature review, as well as analyzing National Health and Nutrition Examination Survey 2013 to 2014 (NHANES) data to access the relationship between dichlorophenol (DCP) pesticides and renal function. Renal function is going to be evaluated by measuring serum creatinine in the blood.

The pesticides used in Central America are no longer used in the U. S. since most have been deemed health hazards. Therefore, this paper will examine two chlorinated phenol pesticides including 2,4-dichlorophenol (2,4-DCP) which is mainly an herbicidal pesticide and 2,5-dichlorophenol (2,5-DCP) which is the metabolite of 1,4-dichlorobenzene (1,4-D), a product that has several uses and is found in a variety of agricultural products (Ye, Wong, Zhou, & Calafat, 2014). Both chemicals are metabolized on a cellular level then excreted in the urine (Ye et al., 2014); therefore, examination of the subjects will be done through urine concentrations of the metabolites.

Chlorinated phenols are known to cause nephrotoxicity, hepatotoxicity, and neurotoxicity (Vural et al., 2015; Centers for Disease Control and Prevention [CDC], 2011). They are suspected human carcinogens and a known carcinogen in lab animals (CDC, 2011). The U.S. Environmental Protection Agency (EPA) considers DCPs to be hazardous pollutants (Ye et al., 2014).

### **Research Hypothesis**

We hypothesized that urinary DCP pesticides in the NHANES 2013 to 2014 population would be associated with decreased creatinine clearance.

### **Literature Review**

#### **Public Health Impact**

The mortality rate due to unexplained CKD in the Central American countries of El Salvador and Nicaragua are nine to twelve times higher compared to CKD rates in the U.S., and Cuba (Nerbass et al., 2017). Cuba was compared because of geographical similarity and having a sugarcane industry similar to the U.S. Many theories have developed during the time period when this trend became noted and evaluated. CKD is not only prevalent in the male sugarcane worker, as would be expected, but in females and young children as well, leading researchers to question the factors involved in this process (Orantes-Navarro et al., 2017; Valcke et al., 2017). Although the dehydration and heat stress model work well to explain the injury of the sugarcane worker, it does not explain the CKD in women and children who are also afflicted and dying at an early age from the same conditions. This, therefore, would point back to environmental factors causing the CKD (Nerbass et al., 2017). The most plausible cause is exposure to the pesticides used in the sugarcane industry. The pesticide residue would be a secondary exposure factor for the family members of the sugarcane workers who come into close contact with them,

or their clothing (Orantes-Navarro et al., 2017; Valcke et al., 2017). This is comparable to pesticide workers in the U.S. whose spouses also show significantly higher effects of exposure including kidney disease proportionate to their husband's exposure (Lebov et al., 2015). Also, the pesticide levels may be heavily contaminating the soil, and therefore the groundwater due to continued use over time, causing exposure to the local area (CDC, 2011). Young children would be more at risk due to underdeveloped body systems, potentiating the effect of exposure (Ordunez et al., 2018).

### **Exposure Route**

The presence of 2,4-DCP and 2,5-DCP are considerable public health concerns. 2,5-DCP is a metabolite of 1,4-D which is found in agricultural, and pharmaceutical products, moth balls and deodorants for home and industrial uses, and is a part of the manufacture of dyes. 2,4-DCP is used for organic herbicide production, synthesis of antiseptics and pharmaceuticals, and potentially will enter the environment as a by-product from the degradation of the antimicrobial, triclosan. The by-products of chlorination in drinking water and industrial waste water, as well as wood pulp processing contain 2,4-DCP and 2,5-DCP. The U.S. EPA has listed DCPs as hazardous pollutants, of which exposure can occur through diet, indoor and industrial air pollution, the use of consumer products, and pesticides (Ye et al., 2014).

**Dermal exposure.** DCPs are lipid soluble products that are readily absorbed into the body through contact with the skin. This exposure may be direct as in the case of those individuals who apply pesticides, or indirect as in the case of the secondary person who handles contaminated clothing (CDC, 2011; Orantes-Navarro et al., 2017).

**Inhalation exposure.** Inhalation exposure to DCPs occurs through the mouth and nose into the lungs by inhalation of particles. The most likely exposure by this route would be

inhalation of air pollution due to deodorant or moth ball fumes. This could occur in all age groups (CDC, 2011).

**Ingestion exposure.** Ingestion exposure occurs when DCPs are consumed and make their way into the digestive system, where they are absorbed through the intestines. Since DCPs are in such a wide variety of products, ingestion may occur from pesticide residue, by-products from the chlorination of water, and exposure to pharmaceutical products using DCPs (CDC, 2011).

### **Metabolism**

Metabolism of DCPs takes place in the body fairly quickly, with a half-life of DCPs of between several minutes to three and a half hours. The body then excretes the metabolite in the form of glucuronide in the urine (CDC, 2011).

### **Serum Creatinine**

Creatinine is an indicator of the health of kidney function. Creatinine is produced by the body at a regular rate as part of muscle metabolism. It is filtered out through glomerular filtration during normal renal function (CDC, 2013). Creatinine measurement will provide an overall picture of kidney health, determining if DCP exposure has caused kidney damage.

### **U.S./Global Picture**

DCPs are extremely prevalent chemicals throughout the world. Even though they are known to be toxic, and sometimes deadly, exposure is not limited to the U.S. In a recent biomonitoring event, urine samples were collected from study participants in the U.S., Korea, Kuwait, Japan, India, China, Saudi Arabia, Greece, and Vietnam to determine exposure levels throughout various areas of the world (Honda & Kannan, 2017). Samples were analyzed by ultra-high-performance liquid chromatography and electrospray triple quadrupole tandem mass spectrometry.



Results detected 2,4-DCP the most frequently, with a detection rate (DR) of 92.7%. The median detection concentration level for all countries of 2,4-DCP was 0.34 ng/mL, with China having the highest median level of 1.61 ng/mL, and Vietnam having the lowest of 0.10 ng/mL. The U.S. median was closer to the lower side of the distribution at 0.32 ng/mL. It is hypothesized that the high levels of 2,4-DCP are due to high usage of triclosan in personal care products and the use of 2,4-D herbicides. 2,5-DCP was the next most commonly detected compound with a DR of 87.5%. The median detection concentration level for all countries of 2,5-DCP was 1.78 ng/ml. Japan had the highest median level of 15.7 ng/mL, while Korea and Vietnam had the lowest levels (not detectable). The U.S. median was 1.65 ng/mL.

2,5-DCP is the metabolite of 1,4-D which is widely used in home deodorants and moth balls, causing indoor air pollution, the expected main source for high 2,5-DCP percentages. Since DCPs are by-products of both industrial and drinking water chlorination, as well as the processing of wood pulp, there could be multiple sources of exposure and, therefore, contamination with DCPs. Japan had DRs of 2,5-DCP of 100% and 2,4-DCP of 91.7%. This is thought to be due to the extremely high levels of moth balls in Japanese homes. Vietnam had the lowest DR for 2,4-DCP equaling 63.2% and 2,5-DCP equaling 42.1% (Honda & Kannan, 2017).

### **Health Impacts**

Toxicity in the class of chlorinated phenols in general is classified as a known animal carcinogen and a potential human carcinogen by the International Agency for Research on Cancer (IARC) (Ye et al., 2014; CDC, 2016). Industrial toxicity has been noted to cause death within 90 minutes or less, with loss of consciousness beginning the downward spiral of death. In most cases larger than normal lab values of 2,4-DCP were noted in the urine and blood of the victims, although several death cases did not have lab values available. These deaths have

prompted the EPA and the Occupational Safety and Health Administration (OSHA) to eliminate potential industrial exposure by adopting personal protection standards of respirators and special protective clothing. They have made showers more available in the immediate area of exposure risk for decontamination, since exposure would be considered a life-threatening medical emergency (CDC, 2000).

Chronic exposure experiments with lab animals have determined that the kidney and liver both have changes at even the smallest doses, which only become more prominent as the dosage of exposure increases. At the highest experimental doses, the thymus and reproductive epithelium were also affected (Vural et al., 2015). Long term exposure in humans has been thought to be correlated to non-Hodgkin's lymphoma, soft tissue sarcomas, liver issues, thyroid hormone disruption and potential heart disease as well, with the pesticides being excreted in breastmilk (CDC, 2011; Vural et al., 2015). The current research goal is to determine correlation between 2,4-DCP or 2,5-DCP and a rise in serum creatinine, therefore, decreasing creatinine clearance.

### **Methods**

Data were downloaded from the publicly available 2013 to 2014 NHANES. The information obtained from NHANES is population-based, and collected bi-annually from persons living in the U.S. The survey brochures and consents as well as operations manual for the 2013 to 2014 data set is publicly available in their entirety on the NHANES website, which is part of the Centers for Disease Control and Prevision (CDC).

The total NHANES data set for 2013 to 2014 contained 10,175 individuals from the U.S. that were consented and interviewed. The examination portion of the study was carried out at a

mobile examination center where a physical assessment, examination and laboratory data were collected. Urine specimens were carried out on a subset of individual ages six and older.

Of this set of respondents, only 2,063 had serum measurement for 2,4-DCP, 2,5-DCP and serum creatinine. The pesticides are both part of the CDC's biomonitoring program (CDC, 2016).

### **Confounders**

Sociodemographic and socioeconomic information (age, gender, ethnicity, and household income) were collected by interviewers trained using the NHANES Computer Assisted Personal interview (CAPI) software. Ethnicity was coded as non-Hispanic White, non-Hispanic Black, and Mexican American, Other Hispanic and other race, including multi-racial. Age was categorized into 12 to 19 years, 20 to 59 years, and  $\geq 60$  years. Household income was also split into three groups, with incomes between \$0 to \$19,999 making up the low group, \$20,000 to \$74,999 as the middle group, and \$75,000 and above as the high-income group. Mexican American/Other, 12 to 19 years group, and the \$0 to \$19,999 household income group were used as reference groups for the regression model.

### **Measuring DCP and Serum Creatinine Levels**

The pesticides 2,4-DCP and 2,5-DCP were measured in the urine specimens' of 2,063 participants. Evaluation of the urine specimens was carried out by solid-phase extraction coupled to isotope dilution-high performance liquid chromatography-tandem mass spectrometry (Ye et al., 2014). Determination of serum creatinine levels used the isotope dilution mass spectrometry (IDMS) reference method in a DxC800 modular chemistry analyzer (CDC, 2013).

### **Statistical Analysis**

Data analyses were performed using the SPSS version 25.0 (IBM Corp, Released 2016). Descriptive analysis was performed for the entire sample and by gender. Descriptive statistics for continuous variables (age, 2,4-DCP, 2,5-DCP, creatinine) including measures of centrality (mean and/or median) and dispersion (standard deviation or range). Frequency distributions (number and proportion) were computed for categorical variables (gender, ethnicity, and income).

Multiple linear regression was used to determine the impact of 2,4-DCP and 2,5-DCP exposure on serum creatinine levels, controlling for age, ethnicity, and household income by gender. Ethnicity, age, and household income groups were ‘dummy’ coded as they had more than two levels. Tests were two-sided and carried out at the 0.05 significance level. For regression results point estimate (beta) and 95% confidence interval were reported.

## **Results**

### **Descriptive Statistics**

In the sample population of 2,063 subjects, described in Table 1, 53% were female. Approximately 54% of the population was in the age range between 20 to 59 years. The largest percentage of the population (47%) had an annual household income between \$20,000 and \$74,999. Non-Hispanic Whites constituted the highest ethnic proportion of this population (40%).

Table 1

*Descriptive Statistics of NHANES 2013-2014 Study Population (N = 2,063)*

Characteristics	Descriptive
Age (years) Mean $\pm$ SD	43.13 $\pm$ 20.69
Age Group (years)	<i>n</i> (%)
12-19	390 (18.9)
20-59	1117 (54.1)
>60	556 (27.0)
Gender	<i>n</i> (%)
Male	970 (47.0)
Female	1093 (53.0)
Ethnicity	<i>n</i> (%)
MexAm/Other	801 (38.8)
Non-Hisp. White	827 (40.1)
Non-Hisp. Black	435 (21.1)
Household Income	<i>n</i> (%)
<\$19,999	422 (20.5)
\$20,000-74,999	975 (47.3)
>\$75,000	581 (28.2)
2,5-DCP Median (IQR)*	2.5 (9.7)
2,4-DCP Median (IQR)*	0.6 (1.10)

\*(IQR) Interquartile Range

For 2,5-DCP (Table 2, left panel) the highest levels were seen in the 20 to 59 age group for females, and the  $\geq 60$  years exposure group for males. Non-Hispanic Blacks had the highest mean 2,5-DCP levels for both genders. For 2,5-DCP, males in the low income (\$0 to \$19,999) group had the highest serum levels, whereas for females the middle income (\$20,000 to \$74,999) group had highest levels. Similar to the results of 2,5-DCP, 2,4-DCP (Table 2, right panel) had highest levels for males in the  $\geq 60$  years age category while the highest levels for females were in the 20 to 59 years age group. Non-Hispanic Blacks had the highest mean for both genders. The highest serum mean for 2,4-DCP were in males in the low-income bracket (\$0 to \$19,999) while females were in the middle-income bracket (\$20,000 to \$74,999).

Table 2

*Descriptive Analysis of NHANES 2013-2014 Participants of 2,5-DCP and 2,4-DCP Exposure by Gender*

Characteristics	2,5-DCP		2,4-DCP	
	Male	Female	Male	Female
	Mean (Std Deviation)			
Age Group (years)				
12-19	64.50 (441.50)	80.69 (484.81)	2.74 (13.07)	2.38 (8.74)
20-59	98.07 (727.63)	130.34 (1010.46)	3.24 (19.86)	3.58 (18.45)
>60	190.29 (1181.46)	59.03 (233.77)	6.31 (33.43)	2.53 (7.63)
Ethnicity				
MexAm/Other	147.41 (997.73)	80.99 (454.09)	4.59 (26.69)	2.56 (10.61)
Non-Hisp. White	49.15 (313.51)	44.02 (87.82)	2.19 (10.20)	2.23 (10.02)
Non-Hisp. Black	184.16 (1122.53)	257.35 (1566.99)	6.14 (32.48)	5.77 (25.37)
Household Income				
\$0-19,999	114.18 (591.44)	84.94 (373.69)	3.92 (19.26)	2.62 (7.83)
\$20,000-74,999	108.88 (629.60)	154.89 (1095.15)	3.65 (16.45)	4.11 (19.57)
≥\$75,000	82.15 (857.21)	15.42 (58.12)	3.21 (24.10)	1.39 (4.28)

### Multivariate Linear Regression Analysis

For multivariate adjusted linear regression analysis (Table 3) among males, each unit increase in 2,4-DCP the beta predicted a decrease of -.010 with a 95% CI of (-.028, .008) in serum creatinine which was non-significant  $p = 0.278$ . For multivariate adjusted linear regression analysis among females, each unit increase in 2,4-DCP the beta predicted a decrease of -.011 with a 95% CI of (-.025, .003) in serum creatinine which was non-significant  $p = 0.110$ .

Table 3

*Multivariate Regression Showing Association Between 2,4-DCP and Serum Creatinine in the NHANES 2013-2014 Study*

Variable	Males		Females	
	$\beta$ (95% CI)	<i>p</i> -value	$\beta$ (95% CI)	<i>p</i> -value
2,4-DCP	-.010 (-.028, .008)	.278	-.011 (-.025, .003)	.110
Ethnicity				
MexAm/Other *				
Non-Hisp. White	.023 (-.031, .077)	.403	.073 (.031, .115)	.001
Non-Hisp. Black	.147 (.083, .212)	<.001	.170 (.120, .221)	<.001
Household Income				
\$0-19,999 *				
\$20,000-74,999	.012 (-.049, .072)	.703	.018 (-.026, .063)	.423
$\geq$ \$75,000	.028 (-.039, .095)	.409	.004 (-.047, .055)	.875
Age (years)				
12-19 *				
20-59	.194 (.132, .256)	<.001	.095 (.044, .145)	.044
$\geq$ 60	.347 (.277, .417)	<.001	.234 (.177, .291)	<.001

\* reference category

The multivariate adjusted linear regression analysis (Table 4) among males, shows each unit of increase in 2,5-DCP beta predicted a decrease of -.010 with a 95% CI of (-.022, .002) in serum creatinine which was non-significant  $p = .093$ . The multivariate adjusted linear regression analysis among females, shows each unit of increase in 2,5-DCP beta predicted a decrease of -.011 with a 95% CI of (-.020, .002) in serum creatinine which was significant  $p = .017$ .

Table 4

*Multivariate Regression Showing Association Between 2,5-DCP and Serum Creatinine in the NHANES 2013-2014 Study*

Variable	Males		Females	
	$\beta$ (95% CI)	<i>p</i> -value	$\beta$ (95% CI)	<i>p</i> -value
2,5-DCP	-.010 (-.022, .002)	.093	-.011 (-.020, -.002)	.017
Ethnicity				
MexAm/Other *				
Non-Hisp. White	.020 (-.035, .074)	.480	.069 (.027, .111)	.001
Non-Hisp. Black	.151 (.087, .216)	<.001	.176 (.125, .227)	<.001
Household Income				
\$0-19,999 *				
\$20,000-74,999	.009 (-.051, .070)	.768	.016 (-.028, .061)	.471
$\geq$ \$75,000	.023 (-.044, .090)	.500	-.001 (-.052, .050)	.968
Age (years)				
12-19 *				
20-59	.198 (.136, .260)	<.001	.094 (.043, .145)	<.001
$\geq$ 60	.353 (.283, .423)	<.001	.234 (.177, .292)	<.001

\* reference category

## Discussion

The presence of both 2,4-DCP and 2,5-DCP in NHANES 2013 to 2014 specimens provides evidence that human exposure to these chemical compounds continue to be of concern. 2,5-DCP has higher detectable levels of chemical in excreted urine, which would coincide with exposures from water chlorination, certain pharmaceutical products, as well as indoor air pollution from deodorizers (Ye et al., 2014).

The negative regression results for the exposures of 2,4-DCP and 2,5-DCP with serum creatinine was opposite of our research hypothesis. Previous studies have been inconclusive, with some showing kidney damage in lab animals (Vural et al., 2015) and others showing a positive, weak, or no association to pesticide exposure (Valcke et al., 2017).



Previous prospective cohort studies of U.S. farmers have indicated that pesticide use does cause kidney problems (Lebov et al., 2015); however, the pesticides were not specifically named, and therefore the direct correlation between 2,4-DCP or 2,5-DCP cannot be made as a direct link to potential kidney disease.

### **Strengths**

There are several strengths in this study. The data were derived from NHANES which is nationally representative and characterizes both genders, as well as accounts for ethnicity. The study adjusted for age and household income as well. Earlier studies have shown detectable urinary levels of 2,4-DCP and 2,5-DCP in previous years of NHANES data collections (Ye et al., 2014) which have given rise to concern for further examination of health concerns due to chemical exposure.

### **Limitations**

This study had several limitations. The study didn't look specifically at the levels of 2,4-DCP or 2,5-DCP and CKD, but on serum creatinine which is one of several indicators of kidney function. Multiple other factors such as underlying disease factors could affect the interaction between the body's ability to metabolize the pesticide, and serum creatinine levels, which may account for lack of any association.

### **Conclusion**

Pesticide use in the United States continues overall to be of a health concern, as well as the environmental impacts caused by its usage. This should continue to be monitored and addressed by the proper agencies.

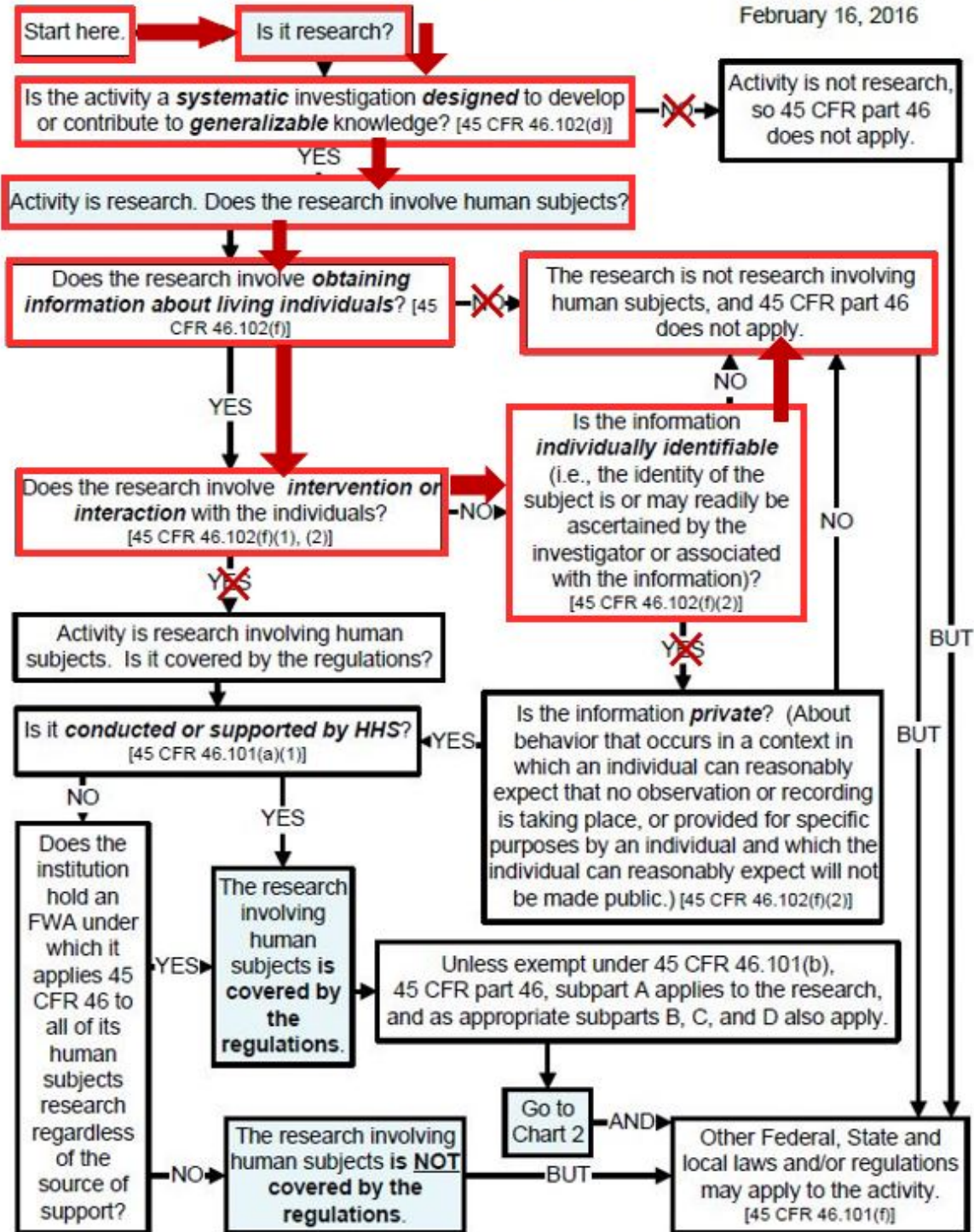
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Appendix A: Human Subjects Regulations Decision Chart

**Chart 1: Is an Activity Research Involving Human Subjects Covered by 45 CFR part 46?**



## Appendix B: List of Competencies Met in Integrative Learning Experience

## CEPH Foundational Competencies

<b>Evidence-based Approaches to Public Health</b>
2. Select quantitative and qualitative data collection methods appropriate for a given public health context
3. Analyze quantitative and qualitative data using biostatistics, informatics, computer-based programming and software, as appropriate
4. Interpret results of data analysis for public health research, policy or practice
<b>Communication</b>
19. Communicate audience-appropriate public health content, both in writing and through oral presentation

## WSU MPH Population Health Concentration Competencies

2. Demonstrate application of an advanced quantitative or qualitative research methodology.
3. Demonstrate the ability to contextualize and integrate knowledge of specific population health issues.