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Literature-Based Health Risk Analysis on Long-Term Pharmaceutical CCP Storage Temperature Exposure on Warehouse Operator

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Abstract. *Warehouse operators working in pharmaceutical Cold Chain Product (CCP) storage areas are frequently exposed by low temperatures ranging from 2 to 8°C. This condition may affect the operators' long-term health condition since there are no operational standards in companies or regulators that regulate the operator changes schedule on CCP area. This narrative literature-based risk analysis was performed using articles collected from Taylor and Francis, ScienceDirect, and Google Scholar databases published around 2025-2026. From five included studies, various health conditions were classified to four severity levels (negligible, minor, moderate, and severe). It ranged from reversible responses, such as decreased skin temperature and minor respiratory infections, to moderate and severe conditions involving cardiovascular and respiratory impairment, as well as cellular apoptosis. The risk analysis proves that cold exposure may lead to cumulative physiological stress and progressive health risk. These findings are considerable for regulators to ensure occupational safety regulation on CCP environments.*

Keywords: *Cold Chain Product; Literature-Based; Operators' Health; Risk Analysis; Storage Room.*

1. INTRODUCTION

Pharmaceutical Distributor is a licensed pharmaceutical company responsible for the pharmaceutical product supply chain. These companies' operations include procurement, storage, and distribution of pharmaceutical products and pharmaceutical raw materials in huge amounts. The compliance of these companies should be provable according to local regulations (BPOM RI, 2025). Indonesia's local statute on GDP (Good Distribution Practice) had mentioned Cold Chain Product (CCP) handling in one focused part. One of the GDP requirements for CCP handling is to perform a specific training for operators working in the cold room. It requires the capability and skills of the operators to not only manage the products stored in cold rooms but also be responsible for its temperature monitoring (Feyisa *et al*., 2021). Those responsibilities are essential for maintaining product quality by preventing temperature excursions that may compromise product stability. Product quality degradation may affect the patient's safety if it's not quickly detected (Iyer and Robb, 2025).

Cold chain pharmaceutical products include vaccines, biological products, insulin, monoclonal antibodies, certain injectable medicines, and temperature sensitive diagnostic reagents. There are at least three categories of personnel involved in this storage system which are cold chain technician, cold chain picking operator, and the cold chain transporter. Those operators are fully responsible for the end to end CCP process (Nyirimanzi *et al*., 2024). However, the pharmaceutical cold chain extends beyond distribution centers, encompassing manufacturing facilities, transportation systems, hospitals, pharmacies, and other healthcare

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facilities. Consequently, a wide range of personnel may experience repeated occupational exposure to refrigerated environments while ensuring the integrity of temperature-sensitive products. Despites, not all healthcare professionals are aware of the impact associated with cold chain failure. Besides, there is also no one aware of the impact of cold chain temperature exposure on all kinds of people working on it for a long term of time (Ilyass *et al*., 2025).

WHO regulations already mention that "Safety procedures should be in place relating to all relevant personnel and property, environmental protection and product integrity" (WHO, 2026). Current GDP guidelines primarily emphasize product integrity and operational procedures, whereas explicit recommendations regarding the potential long-term health effects of occupational cold exposure remain limited. This review aims to synthesize current evidence regarding the long-term physiological effects of occupational cold exposure among pharmaceutical cold chain personnel and to provide scientific evidence that may support future occupational health policies and GDP revisions.

2. LITERATURE REVIEW

Cold Chain Product (CCP) distribution refers to the transportation and storage of temperature-sensitive pharmaceutical products under controlled temperature conditions throughout the supply chain, from manufacturing to the point of administration or consumption. Maintaining the required temperature range is essential to preserve product quality, safety, and efficacy, thereby ensuring that patients receive products that meet regulatory quality standards. Failure to maintain the cold chain may lead to product degradation, reduced therapeutic effectiveness, and potential risks to patient safety (Jin *et al*., 2026). In pharmaceutical distributors, CCPs should be stored in dedicated cold rooms maintained at temperatures between 2-8°C before patient usage. These cold rooms are designed to provide a stable storage environment that complies with GDP requirements. Personnel working in these facilities are responsible for receiving, storing, monitoring, picking, dispatching, and reporting the temperature-sensitive products while ensuring continuous temperature control (Kumar and Jha, 2017).

In order to support these operations, pharmaceutical companies establish Standard Operational Procedure governing both product handling and personnel safety. Among the routine operational activity performed within cold rooms, order picking is one of the most frequent and physically demanding tasks. Previous research reported that a single order-picking process lasts approximately 20 minutes on average, with a median duration of 15 minutes, during which operators remain continuously exposed to refrigerated conditions. Although

individual exposures may appear relatively short, the cumulative duration over multiple work cycles may be substantial (Ranasinghe *et al*., 2025).

Exposure to cold environments triggers several physiological responses that help maintain core body temperature. These responses include peripheral vasoconstriction, increased metabolic activity, and cardiovascular adjustments such as heart rate changes (No and Kwak, 2016). In fact, this might endanger personnel that are constantly working for a long period of time. Despite the widely spread implementation of CCP systems, the latest guidelines and published literature predominantly focus on product quality maintenance, temperature integrity, and regulatory compliance. It had less attention on the long term potential physiological effects on constant occupational cold exposure among personnel working in pharmaceutical cold chain facilities. Therefore, understanding these potential health effects is important to support evidence-based risk analysis and strategies to overcome it using future GDP recommendation (Chhay & Scheckelhoff, 2023).

3. RESEARCH METHOD

This risk analysis was conducted similar to the narrative review method due to the difficulty of finding the articles related to the topic. Data collection performed by searching on databases such as Taylor and Francis and ScienceDirect. To complete the grey area of data collected, data searching through Google Scholar also performed. The article search was conducted using keywords as "(cold exposure OR low temperature) AND (physiological effect OR health impact) AND (exposure duration) AND (indoor)" After all the articles collected, a further selection was conducted according to inclusion and exclusion criteria in order to get the most relevant article. The inclusion criteria were full access articles, related to cold temperature effect on health, and published in 2025-2026. Meanwhile, the exclusion criteria were not an animal study and the temperature mentioned was below 2°C or over 10°C. The upper limit of temperature criteria is not 8°C chosen because there are temperature changes from cold room to the precondition room (±15°C). The data analysis method was conducted by firstly fragmenting the temperature range 2-10°C to three cold exposure levels which are 2-4°C as severe cold, 5-7°C as moderate cold, and 8-10°C as mild cold. Not only classify the temperature range, the classification was also done on the physiological conditions severity. The classification divided to "Negligible" for condition occur as normal physiological response without causing any harm, "Minor" for mild symptoms that are reversible and won't need medical interventions, "Moderate" for conditions disrupting performance and need mild

medical evaluations, and lastly "Severe" for conditions followed by chronic/serious impact threatening operator's safety.

4. RESULTS AND DISCUSSION

From 70 Taylor and Francis database's articles and 1,545 ScienceDirect database's articles collected, only 4 articles are included. A different combination of keywords were already tried in the searching process, but the more specific keywords did not come with expected articles. The additional article search on Google Scholar also just resulted in 1 additional reference. Data collected from articles were then analyzed.

Table 1. Articles' Exposed Temperature, Time of Exposure, and Health Impacts on Human

References	Exposure Time	Exposed Temperature (°C)	Health Impact
Lin *et al*., 2026	3 hours per day	4	Hypertension; Intestinal Inflammation; Apoptosis;
Weidmann, 2025	6 hours per day	6	Cardiovascular Diseases; Respiratory Tract Infection
Yan *et al*., 2026	n/a	3	Arrhythmia
Rafieian *et al*., 2026	n/a	<10	Spanning Musculoskeletal; Angina Pectoris; Myocardial infarction; Hypertension; Congestive Heart Failure; Atrial Fibrillation; Arrhythmia; Respiratory Tract Infection; Asthma; COPD
Rafieian *et al*., 2025	90 minutes per day	10	Hypertension; Skin Temperature Decrease

A further analysis was then performed using the collected data on Table 1. This analysis resulted in a classification of health conditions by its severity level.

Table 2. Severity Analysis of Health Conditions and the Temperature ExposedUsing the predefined severity classification, the observed health effects reflect a gradient of physiological stress, ranging from adaptive responses to critical conditions.

Severity Level	Physiological System	Conditions	Temperature Range (°C)
1 (Negligible)	Thermoregulatory	Skin Temperature Decrease	10-Aug
2 (Minor)	Respiratory	Respiratory Tract Infection	10-Jun
3 (Moderate)	Respiratory	Asthma	10-Feb
	Cardiovascular	Hypertension	10-Feb
		Angina Pectoris	10-Feb
	Musculoskeletal	Musculoskeletal Spanning	10-Feb

	Gastrointestinal	Intestinal Inflammation	4-Feb
4 (Severe)	Cardiovascular	Myocardial Infarction	10-Feb
		Arrhythmia	10-Feb
		Congestive Heart Failure	10-Feb
	Cellular	Apoptosis	4-Feb
	Respiratory	Chronic Obstructive Pulmonary Disease	10-Feb

Negligible Level

Skin temperature decrease is the only condition showing negligible effects which represent a normal thermoregulatory response of the body under mild cold exposure. The skin temperature is usually going down for more than 5°C in only one hour of cold exposure (Rafieian et al., 2026). Fingers and hands skin will be the body area with the highest temperature decrease compared to other body parts. It also gives a relation to human cognitive performance that might affect the operator's performance on the job (Sun et al., 2025). Normally, skin temperature will be back to the normal level in 20 minutes that shows this condition is reversible in a short period of time (Mifsud et al., 2022).

Minor Level

The other classification is Minor level. The only condition classified as Minor severity level is respiratory tract infections. The lower the temperature exposed operator, the higher possibility of infections may occur on their respiratory tract. The possibilities come from the effect of mucociliary clearance (MCC) function impairment due to cold temperature (Lee and Yoon, 2024). This condition is included as Minor because as soon as the mucociliary can normally functionize again the body protection on respiratory tract infection is also back to the normal state.

Moderate Level

Different with the negligible and minor severity level conditions, the moderate level includes four physiological systems responses such as respiratory, cardiovascular, musculoskeletal, and gastrointestinal. In the musculoskeletal system, cold may decrease the power and contraction velocity of muscle with also increase tendon stiffness (Farbu *et al*., 2024). In the gastrointestinal system, the disruption of normal gut flora is the main cause of its inflammation happening under the cold temperature (Lin et al., 2026). In the respiratory system, further effects may happen due to MCC function impairment associated with inflammation in the respiratory tract is cold-induced asthma. The MCC impairment may result in thick mucus plugging on the tract and narrowing the airway (Rafieian *et al*., 2026). Lastly, the cardiovascular system is affected in the form of hypertension and angina pectoris for a moderate level. A cold-induced elevation of blood pressure happened due to the spontaneous

response to increasing body temperature while the blood vessels are narrowing (vasoconstriction) (Lin *et al*., 2026). These conditions may be reversible, but the impact to the performance and need a further medical evaluation to prevent it leads to worse conditions.

Severe Level

This highest level, which is Severe, of effect is associated with irreversible cardiovascular, cellular, and respiratory diseases. Conditions happening in the severe level lead to serious or chronic stage and may threaten the operator's safety. These severe conditions are associated with three essential systems in the human body which are cardiovascular, respiratory, and cellular systems. The cold-induced cellular disruption occurs as a result of oxidative stress. The myocardium apoptosis leads to mitochondrial damage and myocardial dysfunction (Cong *et al*., 2018). Not only come as the effect of cellular impairment, the cardiovascular disruption also may be directly caused by the cold temperature. Cold stress might trigger the electrophysiological system causing arrhythmias or even Sudden Cardiac Death. Cold also increases the myocardial oxygen demand leading to infarction or ischemia (Li *et al*., 2026). In addition to vasoconstriction on the cardiovascular system, the cold temperature also induces a bronchoconstriction on the respiratory system. This leads to exacerbation such as COPD (Sohail *et al*., 2023).

These findings indicate the correlated progressive physiological reaction. The initial thermoregulation response in negligible level possibly happened after a minimum 90 minutes per day of exposure (Rafieian *et al*., 2026). It may develop to the minor and moderate level of organ function disruption or even reach a severe level of conditions when the warehouse operators are exposed to the cold temperature for a long period of time reaching more than 6 hours per day (Weidmann, 2025).

5. CONCLUSION

From this health risk analysis, the long-term cold temperature effect which exposed the warehouse operators in the pharmaceutical cold chain product storage area may occur in several health conditions. These are classified in thermoregulatory, gastrointestinal, respiratory, cellular, and cardiovascular systems with different severity levels. A long-term exposure more than 90 minutes daily may lead to the more severe condition cumulatively.

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