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RESEARCH ARTICLE

In vitro study design derived from an in vivo lifting task

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Abstract

Biomechanical properties of the spinal tissue constituents, especially in the intervertebral disc (IVD), contribute to disability and high costs. The IVD is considered to be one of the main etiologies of chronic low back pain. Changes in the biomechanical properties of the spine, especially in the IVD, are related to multiple factors such as type and duration of loading, recovery periods, osmosis, relaxation, and diffusion processes. To quantify spinal burden in vivo, various dose models have been developed in the context of ergonomics research. In our work both in vivo and in vitro studies were conducted to investigate the effects of loading and rest periods alteration on mechanical properties of the spine. A multibody simulation (MBS) was used to translate the collected motion data from the in vivo study into forces and moments as boundary conditions for the in vitro study. An in vitro spine test rig is used to apply axial compression forces and pure moment loading in flexion/extension direction to spinal segments according to the conditions that have been determined in the MBS. In this article, an approach is presented to coordinate the boundary conditions in vivo and in vitro in order to carry out a holistic investigation. In addition, it is shown why cyclic preconditioning seems to be a more suitable preparation of the samples compared to a constant one in this experimental context.

1 | INTRODUCTION

High mechanical loads on the spine represent one of the main factors causing back pain, for example, as the result of lifting tasks or carrying heavy loads [1]. Acute low back pain is prevalent and, especially when it becomes chronic, is a major cause of absence from work [2, 3]. The intervertebral disc (IVD) is considered one of the most common sources of this chronic pain in adults, but it remains unknown which mechanical conditions are mainly responsible for its degeneration [4, 5]. Multiple factors such as type and duration of loading, recovery periods, osmosis, relaxation, and diffusion processes are considered to have an influence on the biomechanical properties of the spine, especially in the IVD [6, 7]. To gain insight into the mechanisms in the IVD, accurate mechanical characterization is necessary to analyze and understand

injury mechanisms, aging effects, and changes in the material properties of the various tissue structures [8]. For this, a biomechanical ex vivo approach is unavoidable, since many parameters of measurement cannot be determined in vivo in addition to experimental limitations regarding loading duration and intensity [1]. In the context of the laboratory, despite influencing factors that cannot be mapped in vitro, such as healing and long-term effects, many factors influencing the experimental results exist that have to be taken into account when analyzing the results and transferring them to the clinical setting [9]. These include, for example, the application of a physiological preload, test speed, humidity conditions, test temperature, exposure duration, and the number of test cycles [9]. Therefore, in vitro conditions need to mimic all aspects of in vivo conditions to the maximum extent possible [9, 10]. Holsgrove et al. suggest testing the specimens dynamically in a 37°C test fluid under axial preload [9]. Applying a preload is relevant because the spine, and thus the IVDs, are subject to compression forces due to the body weight and muscle force, and additionally due to external loads [11]. The pressure in the nucleus pulposus can be measured to approximate physiological axial compression conditions [11]. On the other hand, before starting experiments, the IVD hydration level requires to be brought to a physiological level [12]. Using a liquid environment is one way to prevent specimen dehydration, but specimens will swell if not constrained, for example, by imposing axial compressive force [11]. This hyperhydration affects the energy absorption of the specimens and changes the dynamic properties and stiffness [11]. Schmidt et al. [10] were able to show that preparation and preconditioning and/or an appropriate pressure and osmolarity of the culture media lead to a reduction of the initial disc hydration and/or fluid transport, resulting in a complete recovery of the disc height in vitro. There is no consensus in the scientific community on the duration of a static compression test, but the larger portion indicated a duration of 8 h or longer [11].

The measurement of parameters inside living human subjects requires a high degree of effort and preparation in the clinical setting, which is why indirect measurement methods are often used in vivo [13]. Currently, a complete replication of the in vivo conditions is not achievable because the real forces and moments in all degrees of freedom are unknown and the test systems have limited ability to replicate the real conditions inside the body [11]. Performing either in vivo or in vitro studies offers both advantages and limitations. Therefore, both study types were combined to be able to finally use the results for conclusions in vivo.

Given the nature of most occupational settings, individuals are usually exposed to multiple work-related risk factors, and from an ergonomics perspective, the question of the relative importance of various risk factors of work-related exposure is a very relevant question [14]. In this work, we propose cumulative loading doses that are subsequently used [14, 15] to study the change of the mechanical spinal tissue properties experimentally in the context of ergonomics. However, there is currently no standardized method for calculating cumulative loading, and the question remains on how the interaction of both, the intensity and temporal aspect, should be interpreted in terms of the cumulative loading dose that an individual is exposed to [14]. The accuracy of the dose model considered is crucial in obtaining reliable results for assessing a workplace and making informed decisions within the ergonomic intervention process [16] and a lack of standardization could lead to both evaluation results of comparable working conditions being different and evaluation results of different working conditions being comparable only if the calculation method is identical [17]. As empirical evidence from both in vivo [18] and in vitro [13] investigations suggest the use of a weighting for the factor load intensity relative to load duration, several weighted calculation methods were proposed [14].

In this article, special focus is given to the study design developed to compare in vivo and in vitro conditions. This includes preconditioning, a crucial prerequisite for generating measurement results comparable to in vivo conditions. The in vivo study was conducted first to determine boundary conditions for the in vitro study using MBS. For the in vitro study, a test rig for conducting mechanical in vitro experiments on spinal cadavers was used [19, 20]. Compared to the in vivo study, a longer exposure duration is selected to investigate its influence on the measured variables. Before starting the loading sequence derived from the in vivo lifting task, preconditioning is performed. At the end of the experimental period, an endurance test is conducted to provoke damage. The objective is to investigate the effects of loading and rest periods on the change in mechanical properties of the spine. Findings can be used to optimize ergonomic assessment methods.

This article is organized as follows: Section 2 introduces the considered in vivo lifting task and its MBS. Section 3 discusses the design of the in vitro experiments and the preparation of the specimens. It also compares two approaches for specimen preconditioning before the applications of the moments in flexion and extension direction take place. In Section 4 we conclude the article with a brief discussion.

2 | IN VIVO LIFTING TASK AND ITS MBS

2.1 | Dose models in the context of an in vivo lifting task

For the ergonomic assessment of manual lifting, the peak and cumulative spinal compression force in segment L5/S1 is seen as one relevant parameter. While peak force risk seems to be well-studied, the influence of cumulative force is not. This ergonomic assessment method in which multiple risk factors are relevant by definition since the concept follows the underlying principle of integrating physical loading over time [21]. Therefore, both the intensity and temporal aspect of the load are taken into account [21]. As elaborated by Garg und Kapellusch [22], methods based on the concept of cumulative loading are potentially more appropriate to assess physical exposure in the workplace than both peak- and average-based assessment methods, as these risk systematic over- or underestimation.

A frequently used calculation method for determining a work-related dose of physical stress is the calculation method proposed by Jäger et al. [13, 23], in which the intensity of the stress is squared relative to the duration of the stress. According to this method, the daily dose

$$TD_j = \sqrt{\sum_i \frac{(F_i^2 \cdot t_i)}{8\ \mathrm{h}}}\ 8\ \mathrm{h} = \mathrm{const.} \tag{1}$$

is based on the average and process-specific IVD pressure force F_i during an 8 h shift and the respective process duration t_i.

The work activity of the in vivo study consists of a lifting task since this movement is of particular importance in the context of work-related physical exposure [24]. The participants are asked to lift and descend various weights during a defined period of time. Rest periods are provided between the individual load phases. Overall, different loading scenarios were performed in which the total load as well as the total break time are the same. In this article, however, the focus is placed on one sequence, which is shown in the top part of Figure 1. After starting with the largest load of 6 kg for a duration of 4 min (two times 2 min), a pause follows (two times 2 min). Then the load of 4 kg is lifted for 6 min and after another break the load of 2 kg is lifted for a total of 8 min. Details in the in vivo study are presented in ref. [25].

2.2 | Multibody simulation

The data from the in vivo experiments were used in a MBS. The experiments were implemented virtually in the software Anybody and the standard model was extended to the experiment. Thus, taking into account the muscle-tendon forces, the occurring moments between the individual segments could be determined. The moments that have been determined

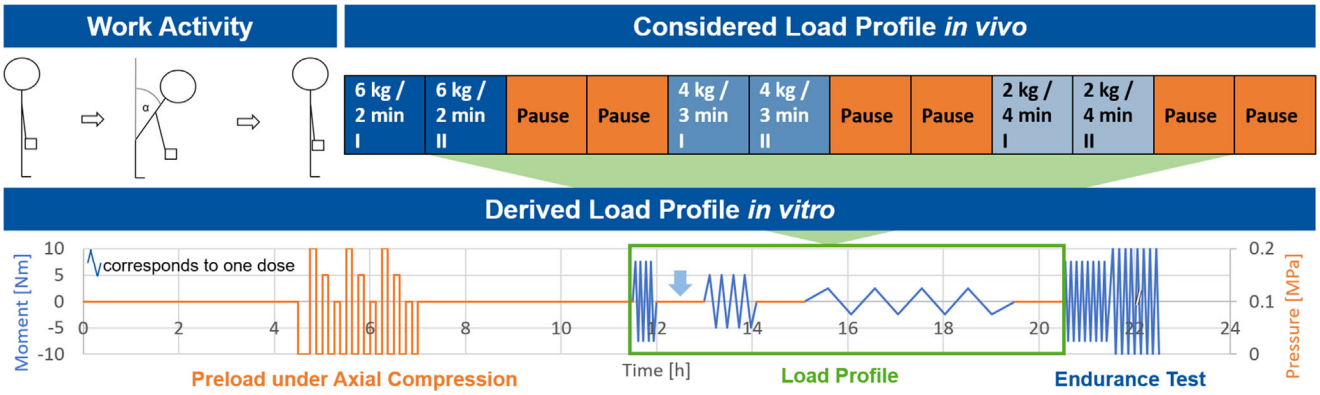

FIGURE 1 Schematic draft of the study design: Top: in vivo study lifting task sequences, consisting of three different loading periods for a defined duration, divided by pause times. Bottom: Loading sequence for in vitro study, which consists of a preconditioning period (orange), the load profile that has been derived from the in vivo study (green box), and the subsequent endurance test.

with the help of the MBS were compared to values from the literature and used as boundary conditions for the in vitro study [11].

3 | IN VIVO EXPERIMENTS

3.1 | Experimental setup

The Institute of General Mechanics of RWTH Aachen University has developed a test rig that allows loading spinal tissue under physiological conditions [20, 26]. The latest extension of the test rig has been described and illustrated in [19], and it includes the addition of an axial compression cylinder including a follower load principle system (FLPS) that permits specimen preconditioning and cyclic and static loading on the same test rig in a liquid environment at body temperature. A new pressure monitoring device is introduced to track the pressure development in the nucleus pulposus in order to get insight into the material behavior and loading response of the IVD during various loading situations and rest periods.

3.2 | Specimen preparation

Three lumbar calf spines were selected and two-segment specimens, consisting of three vertebrae and two IVDs, were extracted to perform the experiments. The size of the calf spine vertebrae is comparable to that of a human adult. Information on the gender and exact age of the calves is not available, although it has to be pointed out that the mechanical properties of the tissue depend on these factors. Magnet tracking sensors have been attached to the vertebral bodies in order to track their motion. A FLPS has been attached to the specimens that counter the tendency of buckling of the spine due to axial loading. With the help of injection needles (needle size 18G x 2") two holes were placed into the upper and lower IVDs that allow inserting fiberoptic microcatheters into each nucleus pulposus. More details concerning the positioning of the microcatheters can be seen in ref. [19].

To fix the position of the sensors, 3D-printed holders specially designed for this purpose were sewn onto the specimen (see Figure 2). After inserting the sensors, the pressure values are set to zero. Then the specimen is placed in a bellows system filled with phosphate-buffered saline solution with protease inhibitors [27], which keeps the tissue hydrated and decreases tissue degradation. The fluid temperature is kept constant at 37°C. For details on the tissue preparation, we refer to ref. [19].

3.3 | Loading protocol derived from in vivo study

The loading protocol for the in vitro experiments consists of three phases, which are illustrated in the bottom part of Figure 1. In these phases, either applied pure moment loading in flexion and extension ("Flex/Ex") direction (left y-axis in blue, where one amplitude corresponds to one dose) or the intradiscal pressure in the upper disc (right y-axis in orange) are used as main control parameters.

First, the preconditioning is conducted by applying an axial compressive preload to the specimen until a pressure of 0.1 MPa is reached in the upper nucleus pulposus. This value for intradiscal pressure corresponds to the pressure in the nucleus pulposus of a human in the supine position [28]. The axial compression force measured at this moment is kept at a constant level for the following 4.5 h. For this reason, after a pause of 15 min, three axial compression cycles are performed using the pressure values of 0.2, 0.15, and 1.0 MPa for 7.5 min each, interrupted by a pause without compression for 7.5 min. After this procedure, another 4.5 h of constant compression is applied using the same procedure as at the beginning of preconditioning.

During the loading profile phase, a pure moment loading at a rate of 6°/s is applied in flexion and extension direction, corresponding to the dose model used. The higher the load magnitude, the shorter the load duration, resulting in the same value for a dose. Using the values obtained by the MBS and the same dose level for all loading cycles, the loading duration can be calculated using Equation (1) [23]. The procedure begins with four doses of 7.5 Nm pure moment loading in Flex/Ex direction for 29.388 min. After a pause of 1 h during which the compression force is kept constant at the achieved level while a pressure of 0.1 MPa is measured in the upper disc using the same approach as during preconditioning, the next

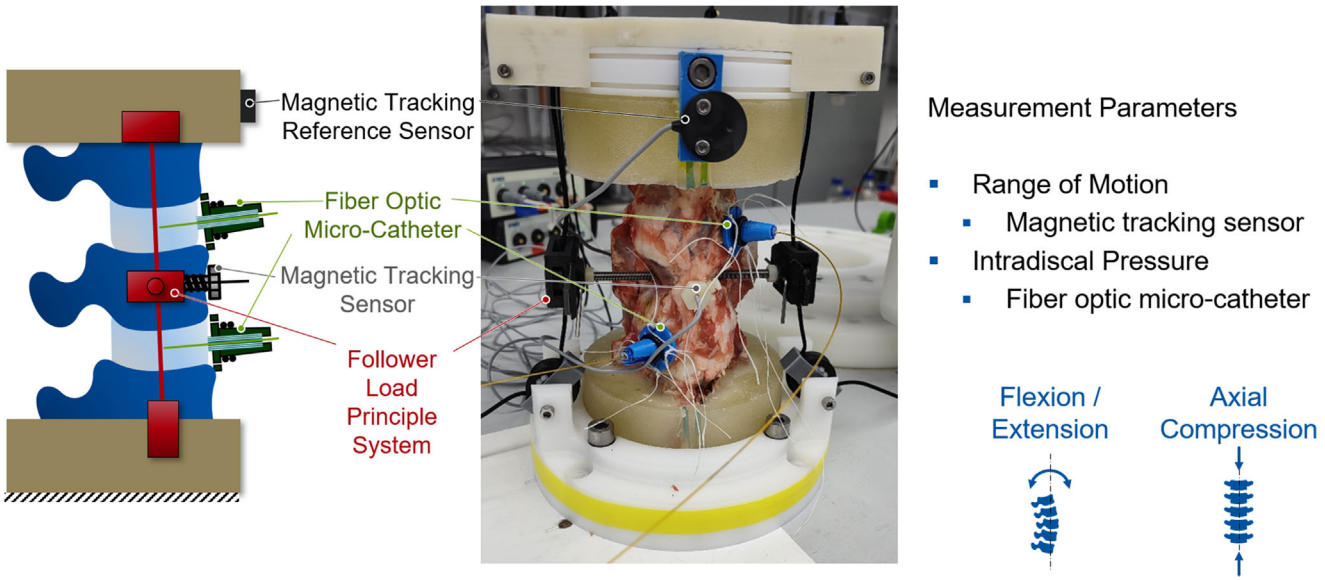

FIGURE 2 Measurement set-up for in vitro experiments. Adjusted mounting system for fiber optic sensor attachment consisting of two divided 3D-printed half-shells. First, injection needles (needle size 18G x 2") are positioned with the tip of the needle in the center of the nucleus pulposus, then the mounting is placed around it and sutured to the tissue of the sample. The needles are removed and the fiber optic sensor is inserted into the disc instead. The tape is positioned around the fiber at the appropriate distance to target the center of the nucleus pulposus. The sensor mounting is positioned around the tape and the two half-shells are pressed together using O-rings around the tape so that the sensor remains in the correct position due to friction.

loading cycle consisting of four doses of 5 Nm is performed for 66.122 min. This is followed by another rest period, then four doses of 2.5 Nm in Flex/Ex direction for 264.49 min, ending with another 1-h rest.

The third phase is an endurance test designed to provoke damage to the specimens. To compare the development of spine properties with the first loading cycle of the loading profile, this phase starts with eight doses of 7.5 Nm pure moment loading in Flex/Ex direction for 58.776 min, followed by 16 doses of 10 Nm for 66.122 min.

3.4 | Comparison of two approaches for preconditioning

Two different approaches of preloading under axial compression were tested and performed. Both approaches were performed for the same duration.

In the first approach, a constant axial compression force measured at a pressure of 0.1 MPa in the nucleus pulposus of the superior disc was applied. For the constant preconditioning in Figure 3A, the force values in blue show recognizable fluctuations, especially at the beginning, but also in a reduced form in the further course. The changes in the compression forces are transferred to the pressure values. Those fluctuations for the constant preload can probably be attributed to adjustments of the axial compression cylinder due to creep effects. The compliance of the tissue ensures that the imposed force in the cylinder position decreases and thus the cylinder piston is displaced until the force is restored.

To prevent further creep during the loading profile phase, we assume that hydration equilibrium is established under a preload that represents the average value of cyclic loading during the loading profile (see [29]). Due to these findings, a different approach for preconditioning was considered. In the second approach, a cyclic compression load with higher pressures was integrated into the procedure as described in the section before. The measured pressures in the nucleus pulposus and the compression forces during the loading profile for cyclic preconditioning are depicted in Figure 3B. As an example, the measurement results of two specimens after the first loading cycle of 7.5 Nm, during the first pause time (see blue arrow in the bottom part of Figure 1), are considered.

In comparison to the constant preconditioning in the left graph, the compression force values and thus the pressure values for the specimen with cyclic preconditioning in the right graph show, with the exception of a peak at the beginning, a steady progression, and seem to confirm the chosen approach. However, even though the cyclic loading protocol during preconditioning results in a significantly higher load than the constant preload at 0.1 MPa pressure in the nucleus

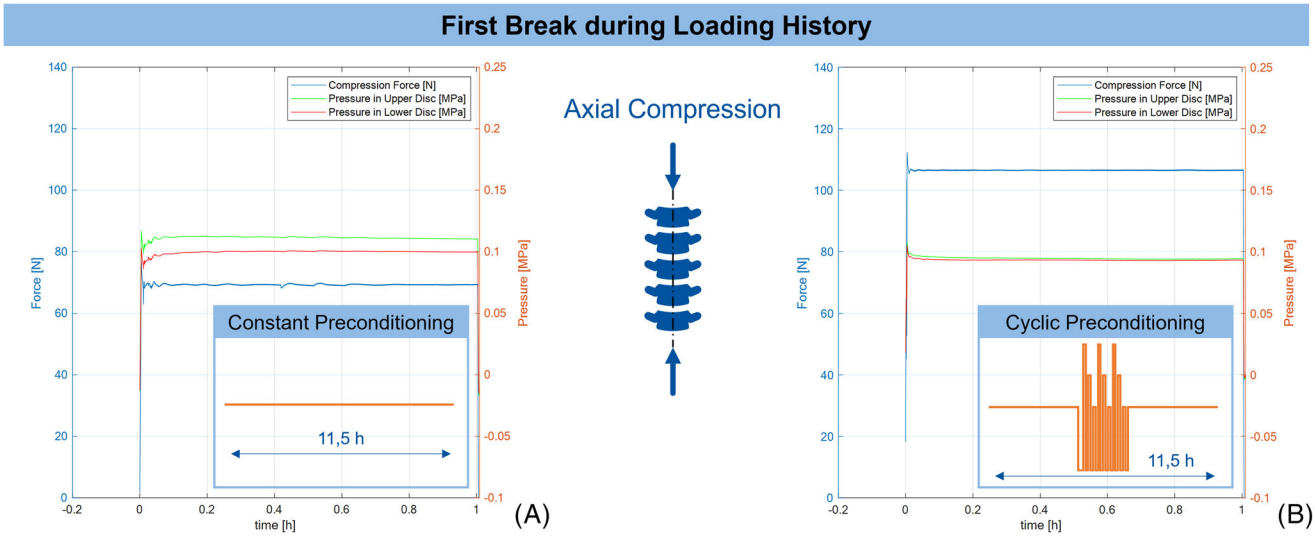

FIGURE 3 Measurement results of two specimens during the first rest period of the Load Profile (see blue arrow in the bottom of Figure 1) to see the influence of preconditioning after the first loading period in flexion/extension direction: (A) Constant preconditioning, (B) Cyclic Preconditioning.

pulposus, in these tests the maximum pressures in the core of the IVD are not sufficient to reach the average pressures during the pure moment tests at ±7.5 Nm as suggested by Schmidt et al. [29].

4 | DISCUSSION AND CONCLUSION

Donated human spines often exhibit large differences in anatomical characteristics as specimens come from donors of different ages and extent of degeneration, for example, due to a different stress and disease history. In addition to the difficulties in comparing measurement data due to these factors, human samples are expensive, available in limited numbers, and are therefore scarce [5]. Therefore, animal models are often used for in vitro testing since they represent the living human disc best among the available options [8]. In addition to their easier availability, the specimens are usually non-degenerated and uniform, thus having a lower standard deviation [8, 30]. This has the potential to help identify the influence of testing techniques with smaller numbers of specimens [30] and may allow effects to be more easily detected due to the smaller variance of individual influencing factors. Using comparative in vitro tests in the thoracic and lumbar regions in all loading directions, Wilke et al. [30] identified calf as a suitable animal model for testing. However, for the results to be applicable to humans, additional comparative testing with human specimens is required.

In our in vitro study, the specimens used were frozen and thawed before testing. The survey by Costi et al. [11] on spine biomechanical testing methodologies shows that 82% of respondents felt that freezing specimens before use was acceptable. Even though this approach is widely followed, it could have an influence on the measurement results. To prove the suitability, more research is needed especially concerning the physiological hydration level, the pressure in the nucleus pulposus, and the influence of preconditioning and preloading processes. The in vitro study should be repeated using fresh specimens to investigate the influence on the mentioned factors.

The study design attempts to closely approximate the physiological experimental conditions for the in vitro study in order to identify common effects between in vivo and in vitro and to allow for translation back to the clinical setting. However, there are some influences that occur in vivo that cannot be reproduced in vitro, such as metabolism and healing effects. Vice-versa, here are phenomena that occur in vitro and which do not correspond to physiological processes such as the autolysis of cadaveric tissue. Additionally, some of the spinous processes and transverse processes including some of the ligaments were removed at the slaughterhouse which can also influence the transferability to the living subject. In both in vivo and in vitro, a precise allocation of load to each component in a biomechanical context is not known in detail and is subject to variation based on individual physiologies. Further research is needed to explore these aspects in more detail. In addition, the position of the pressure sensors was not checked with imaging techniques. The positioning was only done on a visual geometric basis.

Currently, the tensioning mechanism of the ropes limits the maximum axial compression force, as beyond a point the wires slip. Much higher forces are also used in static creep tests under axial compression [11]. In order to provide higher compression forces in the future, this mechanism needs to be adapted. In addition, an extension would be useful to also allow the application of an axial compression force during moment loading in the flex/ex direction. Although this preconditioning approach seems to be a better approximation of the physiological conditions in the living organism, the experimental conditions are still far from the actual fluid flow in vivo. To the best of our knowledge, it has not been possible to reproduce physiological fluid flow in vitro because, on the one hand, the osmotic load in vivo is not known [11] and, on the other hand, there are theories about the influence of threshold pressure [12] and blocked endplates that inhibit fluid flow [10], which hinder implementation in vitro. During this study, only the range of motion during pure moment loading is considered, as well as the pressure values in the IVDs. In order to compare the results with other studies and to gain further insight, the consideration of the change in disc height would also be interesting. In the context of a more physiological approach to the in vitro study, a different dynamic loading pattern than pure moment testing could be considered. Measuring a loading pattern in vivo of, for example, a lifting task and applying it to the specimen in vitro considering combined loading directions could be a future approach.

In future work, the in vivo and in vitro study results will be qualitatively compared to identify similar trends with respect to exposure duration and magnitude in terms of doses [13]. Insights can be used to derive improvements in working conditions.

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