Case Study Summary

Title: Biological Effect Action Level (BEAL) as an Alternative to Biological Exposure Index (BEI)

Version: 1.3

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Introduction: Biomonitoring for Urinary Ni

The main health effects of concern for workers from inhaled nickel (Ni)-containing substances are local respiratory effects (cancer and/or non-cancer), and the most appropriate tool to protect workers from these effects is compliance with up-to-date health-protective breathing zone exposure standards (e.g., Occupational Exposure Limit Values (OELVs). Biomonitoring for urinary Ni can be a useful industrial hygiene tool, for example to assess worker compliance with personal protection equipment. However, no urinary Ni standard can be protective from the potential respiratory effects of Ni, since less-soluble particles containing Ni can remain in the lungs for prolonged periods or cleared without being absorbed. Therefore, urinary Ni standards can be both under- or over-protective from potential respiratory effects of Ni. Since low urine Ni levels do not preclude the existence of increased respiratory toxicity risk from inhalation exposure, and vice-versa, increased urinary Ni levels from non-inhalational sources (such as Ni in diet) does not indicate an increased risk of, for example, tumors in the lung or any other site. This is especially true since Ni compounds have not been shown to be systemic carcinogens (for more information on the health effects of Ni and Ni compounds, please see Buxton et al., 2019).

A systemic health effect of concern that is not specific to workers or the inhalation route is possible reproductive toxicity. Effects on reproduction have been associated with high oral doses of water-soluble Ni compounds in studies with rodents. Although an epidemiological study of highly exposed workers in Russia did not observe these effects, oral reference values for Ni (e.g., the World Health Organization's (WHO) or the European Food Safety Authority's (EFSA) tolerable daily intake (TDI)) are usually based on these effects (see Haber et al., 2017).

A health-based urinary Ni standard could be used to protect from potential systemic health effects of Ni, such as effects on reproduction. While ACGIH published Biological Exposure Index (BEI) values for "Nickel and Inorganic Compounds, Including Nickel Subsulfide" in 2021 (with separate values for exposures to soluble Ni compounds and poorly soluble Ni compounds), these values are based on the relationship between breathing zone Ni levels and workers' urinary Ni levels in various workplaces and have several drawbacks as explained below. NiPERA has been conducting a research program to develop a urinary Ni level tied to a health standard for systemic exposure as opposed to the indirect approach used in BEI determination, a value we call a Biological Effect Action Level (BEAL). This case study summarizes the development and potential implementation of a BEAL in workplaces as an alternative to BEIs to protect against

systemic Ni overexposure. The BEAL can complement but should not replace air monitoring programs that ensure worker safety through compliance with air Ni exposure standards.

1. **Provide a few sentences summarizing the method illustrated by the case study.**

   Workplace air standards are universally used to protect workers from the potential respiratory effects of Ni inhalation (i.e., respiratory inflammation and/or cancer); but there are no biological monitoring standards for Ni linked to systemic health effects. NiPERA has developed an approach to calculate a urinary Ni BEAL that can be used to protect workers from potential systemic health effects of Ni, arising from all possible exposure sources (diet, inhalation, and dermal, in the workplace and at home). This BEAL is linked to a health-based exposure standard such as WHO's or EFSA's TDI. A urinary value (BEAL), corresponding to a TDI can be calculated for each worker with a biokinetic model, considering each worker's characteristics such as body weight and work shift pattern. The individual BEAL can then be used to assess the risk of systemic overexposure to Ni of each worker. This methodology is based on the same concept as the Biological Equivalents approach described by Hayes et al. (2007) that uses established health benchmarks (e.g., TDIs, reference doses [RfDs], or minimal risk levels [MRLs]) to develop screening levels for evaluating biomonitoring data.

2. **Describe the problem formulation(s) the case study is designed to address. How is the method described in the case useful for addressing the problem formulation?**

   ACGIH published Biological Exposure Indices (BEI) for inorganic Ni compounds in 2021, with separate values for soluble and poorly soluble Ni compounds. The BEIs are based on the associations between air monitoring (inhalable Ni particulate in air) and biological monitoring results (Ni in urine) in workers who have been exposed to soluble or poorly soluble Ni substances at the workplace. According to ACGIH, the BEIs were set "to minimize the potential for an increased risk of lung and sinus cancer and the production of inflammatory pulmonary changes." However, no urinary Ni standard can be protective from the potential respiratory effects of mixed exposures to water soluble and insoluble Ni, with different kinetics of absorption and elimination. Low urine Ni levels do not preclude the existence of increased lung cancer risk from inhalation exposure to insoluble Ni, nor do elevated urine Ni levels from oral Ni intake increase the risk of lung tumors (or tumors at any other site since Ni is not a systemic carcinogen, Heim et al., 2007). The most appropriate tool to protect from respiratory effects is compliance with up-to-date health-protective inhalation OELVs such as TLVs, PELs, WELs, etc., and that leaves ACGIH BEIs to play a secondary, and apparently incomplete role in workers' protection in this case.

   Urinary Ni levels reflect systemic exposure to Ni. Urine Ni levels reflect the fraction of Ni that is absorbed into the bloodstream following oral, inhalation, and dermal exposure (although systemic absorption of Ni through the skin is very low, particularly for water insoluble substances ≤0.2%). Larger particles of soluble or poorly soluble Ni compounds (between 15 and 100 µm aerodynamic diameter) are mainly deposited in the upper respiratory tract (i.e., nose and conducting airways region). Most of them will be cleared from the airways and swallowed, where they have the potential to be absorbed through the

gastrointestinal tract. Smaller particles (< 15 µm aerodynamic diameter) that reach the deep lung (i.e., alveolar region) can dissolve and be absorbed into the bloodstream from the lung. Smaller poorly soluble Ni particles can remain in the lung for longer periods of time and potentially cause lung toxicity without appreciably increasing urinary Ni levels. Urinary Ni in the general population predominantly reflects oral exposure to Ni from food, with lower contributions coming from water and air, and even less through the dermal route (De Brouwere et al., 2012). This is because Ni is naturally found in food, particularly in plants. Ni is essential to plants and to some microorganisms in the human gut. Humans ingest 100-150 µg Ni/day from diet, with a relative gastrointestinal absorption of ~5% (De Brouwere et al., 2012). Therefore, setting a BEI for Ni based on the relationship between breathing zone Ni levels and workers' urinary Ni levels is complicated by the different kinetics of water soluble and insoluble Ni absorption, as well as the background level of urinary Ni from dietary intake, which can vary between locations and populations. In fact, the BEI value for poorly soluble Ni compounds of 5 µg/L is within the normal range for populations eating a western diet. This can potentially lead to situations of high numbers of workers out of compliance while not achieving the goal of health protection, since urinary monitoring cannot protect from lung effects of insoluble particles. Oppositely, complying with the BEI of 30 µg/L for soluble Ni compounds may not rule out the risk of overexposure for workers with mixed (soluble and insoluble) Ni exposures by inhalation.

A need exists for a health-based urinary Ni standard to assist in the interpretation of urinary Ni biomonitoring data. However, each workplace has a different exposure profile which, along with geographic differences in dietary intakes, results in very different urine Ni levels. For example, urinary Ni guidance values relevant for metal finishers would not be relevant to alloy workers, and vice-versa, because the underlying differences in the forms of Ni present in the workplace. Therefore, a single urine value (or two values based on solubility such as ACGIH's BEIs) can never be appropriate to protect workers from the potential respiratory effects of Ni in all Ni producing and using sectors.

NiPERA's BEAL is a urinary Ni level tied to a health standard for systemic exposure, such as the WHO TDI for Ni. A BEAL can be calculated for each worker with a biokinetic model, considering each worker's characteristics such as body weight and work shift pattern, and protect from systemic effects from all sources of Ni (inhalation and dietary). The biokinetic model was developed using data from studies of volunteers who ingested known amounts of soluble Ni and then had their plasma and urinary Ni levels monitored over time. It takes into account variability in Ni excretion to predict the average amount of urinary Ni output (for each worker) and its statistical confidence limits following exposure to a given amount of Ni, such as the TDI (Bogen et al., 2021). NiPERA's BEAL value calculated for each worker is therefore a health-based urinary Ni standard that can be used as a screening tool to protect individual workers from systemic overexposure to Ni and complement any industrial hygiene program for Ni.

3. **Comment on whether the method is general enough to be used directly, or if it can be extrapolated, for application to other chemicals and/or problem formulations. Please explain why or why not.**

This approach can be used with any chemical that has an established oral health standard and sufficient kinetic information to be able to predict urinary chemical levels after external exposure. The concept behind the BEAL approach already exists and has been described in the Biomonitoring Equivalent (BE) approach published by Hays et al. (2007; 2008). The BE approach uses pharmacokinetic dosimetry data to calculate levels of biomarkers anticipated to be associated with exposures consistent with general population exposure guidance values (e.g., RfDs, MRLs, and TDIs) and their underlying toxicological points of departure (PODs). This is the basis for putting biomonitoring data into a public health risk context. In our case we applied the approach to workers instead of the general public with a biokinetic model based on studies with human volunteers. While a human PBPK model and an exposure guidance value based on human data is ideal, neither is completely necessary. An exposure guidance value for metals or metalloids based on animal data can be used with information on relevant internal dose metrics in animals or in humans at the POD to inform an internal dose-based BE consistent with the exposure guidance value (Hays et al. 2007; 2008). While not as critical with a metal like Ni that does not undergo metabolism, an understanding of the similarity between human and animal would be important to metals that do undergo metabolism or to organic chemicals.

4. Discuss the overall strengths and weaknesses of the method.

Strengths and weaknesses of BEAL approach in general

Strengths: The BEAL approach links a biomonitoring standard to a systemic health value rather than an air exposure, which is important since urinary Ni levels reflect systemic Ni exposure from all routes of exposure. A BEAL can be indexed to a worker oral reference value (if it exists), to a TDI for the general public (which is conservative for workers), or to a POD as with BE approach. A value is calculated for each worker considering their characteristics and exposure pattern, and result interpretation can be automated with software. The BEAL approach covers all types of mixed exposures to substance of interest.

Weaknesses: The BEAL approach requires a biokinetic model for the substance of interest, and the use of software for BEAL calculation. It requires more information than a spot urine sample (e.g., time from last void, weekly work pattern, weight of worker). The interpretation of the results is more complex since each worker has an individual BEAL level.

Strengths and weaknesses of this particular Ni BEAL

Strengths: The biokinetic model used to calculate Ni BEALs is based on kinetic data from human volunteers at similar exposure levels as the TDI that allows incorporation of inter-individual variation in urinary Ni excretion, avoiding species extrapolation for kinetics. Relying on a TDI set for the general public is conservative for workers but that can be considered in the interpretation phase. Using the Ni BEAL does not require any knowledge about the solubility of the Ni in the potential personal exposures and therefore works for mixed Ni exposures.

Weaknesses: While the biokinetic model for Ni is based on studies with human volunteers, the studies were conducted single exposures with soluble Ni in adults at relatively low exposure levels (≤ 20 µg Ni/kg) with a limited number of subjects (~32). Therefore, the model may not represent the entire population. The kinetics of multiple exposures were estimated with the model and while this is a weakness, the kinetics of soluble Ni absorption and clearance are relatively fast, and therefore confidence in this extrapolation is increased. The Ni BEAL approach currently requires more information than a spot urine sample (e.g., time from last void, weekly work pattern, weight of worker). The Ni BEAL indexes the urine Ni to a reference value for general population rather than for workers, making it a conservative standard. An additional uncertainty is that the critical systemic effect (reproductive toxicity) is based on animal studies with health effects not confirmed in humans.

Strengths and weaknesses of BEI approach for Ni

Strengths: BEIs do not have to be calculated for each worker. They work with spot urine samples. No biokinetic model is needed to implement, and comparison to worker urinary Ni concentration is straight forward.

Weaknesses: BEIs are based on the relationship between breathing zone Ni levels and workers' urinary Ni levels and can be confounded by the background level of urinary Ni from dietary intake. Hand-to-mouth transfer in the workplace and dietary Ni exposure can lead to elevated urinary Ni levels that are not due to elevated air Ni exposure, while the ACGIH BEI for poorly soluble Ni compounds is within the normal background of urinary Ni concentrations. Furthermore, the ACGIH BEI values for Ni derived from relationships between air exposures and urine levels are highly uncertain and can differ by 20-fold. The health protection offered by these values is unclear. Implementing the ACGIH BEIs requires knowledge about the solubility of the Ni compounds the workers are exposed to so that the proper BEI value (soluble or poorly soluble Ni compounds) can be selected as a reference. However, workers are almost always exposed to mixtures of soluble and insoluble Ni compounds, and there is no guidance from ACGIH on how to use the BEIs where there is mixed exposure.

5. Outline the minimum data requirements and describe the types of data sets that are needed.

Generic BEAL Approach:

As in the BE approach, a biokinetic model of some type is needed, which can be based upon kinetic data in animals or humans. According to Hays et al. (2008), this can range from a fully developed PBPK model to simply information regarding biomarker concentration at the point of departure in the key animal study (for the species, strain, and dosing regimen used in the critical study) used in the evaluation of biomarker concentrations in human populations. The use of human or animal data in the derivation of a BE can be informed by available data on the active compound (parent or metabolite, if organic), mode of action, and/or critical

dose metric. In the case of a BEAL, a health-based exposure standard (e.g., TDI, RfD) is needed.

Ni BEAL:

The human biokinetic model for Ni (described in Bogen et al., 2021) was developed and fit to data obtained for 18 human subjects in a study sponsored by NiPERA (Patriarca and Taylor 2010a, 2010b, 2011a, 2011b), and to similar data from an earlier study by Patriarca et al. (1997) with four subjects, and from a study by Sunderman et al. (1989) involving six male and four female subjects. These studies included both urinary Ni excretion and data for Ni in plasma or serum. The resulting human biokinetic model of median urinary Ni in relation to oral dose of soluble Ni used here incorporates a stochastic model of inter-individual heterogeneity in urinary Ni excretion fit to combined NiPERA and Patriarca et al. (1997) data. The stochastic model predicts a 1-tail lower variability bound that is ~4.6-fold less than the model-estimated median urinary nickel level at a specified oral Ni dose

In order to assess the performance of the model with workers' data, a pilot study was carried out with 15 workers at a Ni smelter. A cross-section of workers at the facility volunteered to provide an end-of-shift, end-of-week urine sample to measure their Ni output, as well as provide general information such as work schedule, age and body weight. In this pilot study, the time since last void was noted, and total excreted urine volume and urine density were measured. Using these data, the model was used to predict each worker's urinary Ni output that would be expected from daily workday exposures to the WHO TDI of 11 µg Ni/kg/day. The predicted urinary Ni values (i.e., worker-specific BEAL) were then compared to the measured values to determine if the workers were systemically exposed to Ni levels higher than the WHO TDI. Confidence was increased in the model due to the consistency of the predictions with the measured data without the need to adjust any of the model parameters. A second pilot study is being conducted in a separate workplace to further exercise and evaluate the model.

Does your case study:

A. Describe the dose-response relationship in the dose range relevant to human exposure?

Yes, the biokinetic model was developed from data sets in adults at relatively low exposure levels (≤ 20 µg Ni/kg), we are using an exposure benchmark (TDI) of 11 µg/kg. While background exposures are typically 100-150 µg Ni/day from diet (~2 µg Ni/kg), exposures can be increased in the workplace.

B. Address human variability and sensitive populations?

Yes, to address human inter-individual variability in urinary Ni excretion kinetics, human biokinetic models for Ni were fit jointly to data obtained from 6 human studies consisting of 32 volunteers (Bogen et al., 2021). The studies involved oral exposure to soluble ^{61}Ni, followed by measures of ^{61}Ni excretion up to 72 h after initial exposure. The resulting human

biokinetic model for Ni incorporates a stochastic model of inter-individual heterogeneity in model-estimated urinary Ni excretion.

The endpoint considered (the reproductive developmental outcome is perinatal mortality) is observed in pregnant animals (a sensitive subpopulation) exposed to soluble Ni orally and is a conservative endpoint since no reproductive outcomes have been associated with Ni exposures in human studies with very high workplace exposures to women. It should be noted that the TDIs (WHO, 2007, EFSA, 2020, see also Haber et al., 2017) and therefore the Ni BEAL are not protective of oral exacerbation of Ni dermatitis. This can happen in a subgroup of Ni-sensitive people who also react to oral Ni with an exacerbation of dermatitis at sites of previous contact allergy. Nickel workers are usually screened (via a questionnaire) for Ni allergies (dermal and/or respiratory) prior to employment, and periodically afterwards.

C. Address background exposures or responses?

Yes. A clear benefit of the BEAL approach is the consideration of systemic Ni burden from all routes of exposure, including natural background dietary exposure. Total exposure from background and additional occupational exposure is included in total allowable systemic exposure when compared to the TDI. This is an advantage over the use of a BEI to evaluate urinary Ni levels, which is otherwise complicated by the background level of urinary Ni from dietary intake that can vary between locations and populations. As mentioned above, the ACGIH BEI value for poorly soluble Ni compounds of 5 µg/L is within the normal range for populations eating a western diet. This can potentially lead to situations of high numbers of workers out of compliance while not achieving the goal of health protection, since urinary monitoring cannot protect from lung effects of insoluble nickel compounds.

D. Address incorporation of existing biological understanding of the likely mode of action?

Yes, this approach recognizes that inhalation of Ni can cause local effects on the respiratory tract and systemic effects (like reproductive toxicity by soluble Ni) upon absorption. Since urinary Ni biomonitoring cannot necessarily protect from local lung effects of insoluble nickel compounds, the focus of the complimentary BEAL is to protect from possible systemic effects. The only systemic effect documented in humans is oral exacerbation of Ni dermatitis. While this effect is significant in Ni-sensitive people who also react to oral exposure, the occurrence of this effect is too low and variability is too great on which to base a urinary standard, particularly for Ni workers. Reproductive (developmental) toxicity associated with soluble Ni exposure has been observed in rodents, but a large cohort study of highly exposed female workers in Russia did not demonstrate adverse reproductive outcomes to be associated with Ni exposures. Nevertheless, the Ni TDI is based on these effects and thus a BEAL can be based on the prevention of those effects as if they could occur in humans as a conservative approach.

E. Address other extrapolations, if relevant – insufficient data, including duration extrapolations, interspecies extrapolation?

Because human data are almost always more limited than animal data, the human biokinetic model used here is based on studies with relatively few human volunteers. Therefore, associated predictions of inter-individual variation in urinary Ni excretion extrapolated to a larger occupational population may be limited by small-sample bias. These studies were also conducted with single exposures to soluble Ni, and the kinetics of multiple exposures were estimated with the model. Fortunately, the kinetics of soluble Ni absorption and clearance are relatively fast, thereby increasing the confidence in these predictions. Finally, it is not known if the critical effect that forms the basis of the TDI (reprotoxicity) occurs in humans. Extrapolation of this effect to humans is therefore conservative.

F. Address uncertainty?

ACGIH's BEIs are based on the relationship between breathing zone Ni levels and workers' urinary Ni levels in various workplaces, with separate values for exposures to soluble Ni compounds and poorly soluble Ni compounds, and no consideration of variations in particle size or the presence of mixed exposures to soluble and insoluble Ni particles. Moreover, the correlations between air and urinary Ni in worker studies are highly variable across studies. According to the ACGIH BEI Documentation, the urinary Ni levels calculated from a single air concentration of 0.1 mg soluble Ni/m^3 range from 19.9 – 356.3 µg Ni/L, a nearly 20-fold range. This indicates a large amount of uncertainty related to the correlations between air and urinary levels. This is not surprising because the relationship between air Ni and urine Ni among Ni-exposed workers depends on factors other than the exposure levels and the solubility of the chemical forms of Ni in the air. The particle-size distribution (PSD) of the air exposure plays a key role in determining where the particles will deposit in the respiratory tract, and whether they are likely to be cleared by swallowing (gastro-intestinal absorption) or by dissolution, or they will remain in the lung for longer time periods. Furthermore, both stationary and personal sampling strategies and a variety of different sampling and analytical techniques are used in these studies. Another factor that contributes to workplace urinary Ni is oral exposure via hand-to-mouth transfer. Dust deposited on the face, even when the worker is wearing a respirator, can find its way to the gastro-intestinal tract through poor hygiene practices where it will be absorbed and contribute to urine Ni measurements, further confounding the correlation between inhalation exposure and urinary Ni levels. Smokers often ingest Ni from contaminated hands and mouth. In addition, it is not clear if and what type of personal protective equipment (PPE) was being used in all the studies used by ACGIH. These factors will modulate the fraction of urine Ni coming from air, hand-to-mouth, and diet. Therefore, elevated urinary Ni does not always represent elevated air Ni exposure and/or increased health risks.

Furthermore, workers are almost always exposed to mixtures of soluble and insoluble Ni compounds in the workplace. Therefore, each workplace has a different exposure profile which, along with geographic differences in dietary intakes, results in very different urine Ni levels. For example, urinary Ni guidance values relevant for metal finishers would not be relevant to alloy workers as a marker of air exposure, and vice-versa. Therefore, a single urine value (or two values based on solubility such as ACGIH's BEIs) can never be appropriate to cover all Ni producing and using sectors in all locations. For example, since

ACGIH's BEI value of 5 µg Ni/L for poorly soluble Ni compounds is within the natural background population range of urinary Ni coming from dietary intake, there could be situations of high numbers of workers out of compliance while at the same time not being protected from health effects, since urinary Ni monitoring cannot protect from Ni lung effects. Oppositely, complying with the BEI of 30 µg/L for soluble Ni compounds may not rule out the risk of overexposure for workers with mixed (soluble and insoluble) Ni exposures by inhalation.

Implementing NiPERA's BEAL will require more information on each worker, such as their body weight and weekly work shift pattern, than implementing the ACGIH BEIs. However, this approach does not require any knowledge about the solubility and/or the particle size of the Ni in the potential personal exposures. Implementing the ACGIH BEIs does require knowledge about the solubility of the Ni compounds the workers are exposed to so that the proper BEI value (soluble or poorly soluble Ni compounds) can be selected as a reference. Also, there is no guidance from ACGIH on how to use the BEIs where there is mixed exposure to both soluble and insoluble Ni in a single workplace, which will be the case in many Ni workplaces.

Uncertainty in the BEAL approach includes uncertainty in both the construction of the biokinetic model, its associated inter-individual variability, and uncertainty inherent in setting the TDI. However, there are conservative assumptions built in part which balance the uncertainties. This can also be considered when selecting how to implement the BEAL results in a workplace, as discussed below.

G. Allow the calculation of risk (probability of response for the endpoint of interest) in the exposed human population?

As mentioned above, conservativism is present in both the construction of the biokinetic model and the setting of the TDI for the general population. This conservatism can be considered when deciding how to utilize the modeling results in a workplace. The model can predict the median and 95% upper and lower confidence limits (UCL, LCL) of urinary Ni output at the TDI exposure, and these values can be used in a framework for implementing the BEAL results when compared to measured urine output in workers. One possible framework for interpretation is as follows. If the measured urine Ni output is below the 95% LCL of the BEAL: no action is needed. If the measured urine Ni output is above the 95% LCL of the BEAL: repeat the measurement and watch this worker. Due to the inherent conservatism in the approach, exceeding the 95% LCL of median BEAL prediction is not a cause for immediate alarm. Rather, this could indicate that this worker should be retested and monitored over time. Only if the measured urine Ni output is above the 95% LCL of the BEAL on multiple occasions should the worker be removed from the workplace and an investigation of potential exposure sources both in and outside of the workplace should be initiated. Alternatively, because we indexed the Ni BEAL to a TDI for the general population (calculated as an experimental animal No Observed Adverse Effect Level [NOAEL] divided by an uncertainty factor of 100), it could be possible to indicate that only when the urine Ni is above the 95% LCL of the value corresponding to the POD/50 (using a 2-fold lower assessment factor for the "healthy" workers when compared with the general public) the

worker should be removed from the workplace and an investigation of potential exposure sources should be initiated.

H. Work practically? If the method still requires development, how close is it to practical implementation?

Urinary biomonitoring is a useful tool in the workplace to complement any industrial hygiene program for Ni. It can allow exposure assessment for individuals as well as groups such as work areas or job types. The ACGIH BEI approach of setting urinary Ni levels based on inhalation exposures for soluble and poorly soluble Ni forms is complicated by differences in airborne particulates (e.g., bioavailability and PSD and of the particles) and the fact that workers are often exposed to mixtures of soluble and insoluble Therefore, urine Ni values based on solubility such as ACGIH's BEIs, although practical, will never be appropriate to cover all Ni producing and using sectors in all locations. The most appropriate tool to protect workers from local lung effects is compliance with health-protective breathing zone OELS (e.g., TLVs, PELs, WELs, etc.).

Alternatively, the Ni BEAL approach focuses on the avoidance of systemic Ni overexposure. From a practical point of view, a biokinetic model is necessary to implement the BEAL approach. A biokinetic model for Ni has been published that considers individual variability in Ni excretion (Bogen et al., 2021). The BEAL approach requires a bit more information about worker and urine sample than the BEI approach. However, the BEAL approach does not require information on Ni breathing zone exposure characteristics like those needed to use BEIs. Therefore, the relevance and reliability of results interpreted within BEAL approach are significantly higher than for BEIs.

A pilot study has been carried out with 15 workers representing a cross section of job duties at a Ni smelter. No model parameters required adjustment to predict the measured data, increasing the confidence in the model. Before widespread implementation of the BEAL approach, data from additional workers comparable to those reported here would be valuable to further evaluate the model parameters.

An interpretive framework (e.g., traffic light approach) needs to be established so that the calculated BEAL values can be compared to workers' data. A software tool based on the current model may be developed in which a worker's parameters such as shift, exposure time, body weight, etc. could be entered and a BEAL for urinary Ni concentration for that worker would be automatically calculated and interpreted. Finally, industry and regulatory buy-in on the BEAL approach will be needed for widespread implementation.

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